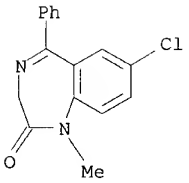
```
Trying 3106016892...Open

Welcome to STN International!  Enter x:x
LOGINID:sssptal617mxb
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Sep 17  IMSworld Pharmaceutical Company Directory name change
                  to PHARMASEARCH
 NEWS  3  Oct 09  Korean abstracts now included in Derwent World Patents
                  Index
 NEWS  4  Oct 09  Number of Derwent World Patents Index updates increased
 NEWS  5  Oct 15  Calculated properties now in the REGISTRY/ZREGISTRY File
 NEWS  6  Oct 22  Over 1 million reactions added to CASREACT
 NEWS  7  Oct 22  DGENE GETSIM has been improved
 NEWS  8  Oct 29  AAASD no longer available
 NEWS  9  Nov 19  New Search Capabilities  USPATFULL and USPAT2
 NEWS 10  Nov 19  TOXCENTER(SM) - new toxicology file now available on STN
 NEWS 11  Nov 29  COPPERLIT now available on STN
 NEWS 12  Nov 29  DWPI revisions to NTIS and US Provisional Numbers
 NEWS 13  Nov 30  Files VETU and VETB to have open access
 NEWS 14  Dec 10  WPINDEX/WPIDS/WPIX New and Revised Manual Codes for 2002
 NEWS 15  Dec 10  DGENE BLAST Homology Search
 NEWS 16  Dec 17  WELDASEARCH now available on STN
 NEWS 17  Dec 17  STANDARDS now available on STN
 NEWS 18  Dec 17  New fields for DPCI
 NEWS 19  Dec 19  CAS Roles modified
 NEWS 20  Dec 19  1907-1946 data and page images added to CA and CAplus
 NEWS 21  Jan 25  BLAST(R) searching in REGISTRY available in STN on the Web
 NEWS 22  Jan 25  Searching with the P indicator for Preparations
 NEWS 23  Jan 29  FSTA has been reloaded and moves to weekly updates
 NEWS 24  Feb 01  DKILIT now produced by FIZ Karlsruhe and has a new update
                  frequency

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 17:04:06 ON 13 FEB 2002
```

```
=> file registry
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.15       0.15

FILE 'REGISTRY' ENTERED AT 17:04:14 ON 13 FEB 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 American Chemical Society (ACS)

STRUCTURE FILE UPDATES:   11 FEB 2002  HIGHEST RN 391593-47-8
DICTIONARY FILE UPDATES:  11 FEB 2002  HIGHEST RN 391593-47-8

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the
CAS Registry Numbers that were added to the H/Z/CA/CAplus files between
12/27/01 and 1/23/02.  Use of the P indicator in online and SDI searches
during this period, either directly appended to a CAS Registry Number
or by qualifying an L-number with /P, may have yielded incomplete results.
As of 1/23/02, the situation has been resolved.  Also, note that searches
conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files
incorporating CAS Registry Numbers with the P indicator between 12/27/01
and 1/23/02, are encouraged to re-run these strategies.  Contact the
CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698,
worldwide, or send an e-mail to help@cas.org for further assistance or to
receive a credit for any duplicate searches.

=> s diazepam/cn
L1            1 DIAZEPAM/CN

=> d

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   439-14-5  REGISTRY
CN   2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-1-methyl-5-phenyl- (8CI,
     9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   1-Methyl-5-phenyl-7-chloro-1,3-dihydro-1H-1,4-benzodiazepin-2-one
CN   1-Methyl-5-phenyl-7-chloro-1,3-dihydro-2H-1,4-benzodiazepin-2-one
CN   7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one
CN   7-Chloro-1-methyl-2-oxo-5-phenyl-3H-1,4-benzodiazepine
CN   7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one
CN   7-Chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one
CN   An-Ding
CN   Ansiolisina
CN   Apaurin
CN   Apozepam
```

CN Assival
CN Atensine
CN Atilen
CN Bialzepam
CN Calmocitene
CN Calmpose
CN Cercine
CN Ceregulart
CN Diacepan
CN Diapam
CN Diazemuls
CN **Diazepam**
CN Diazepam-Lipuro
CN Duxen
CN Eridan
CN Faustan
CN Horizon
CN LA 111
CN Lembrol
CN Levium
CN Methyldiazepinone
CN Methyldiazepinone (pharmaceutical)
CN Morosan
CN Noan
CN Org 2447
CN Paxate
CN Paxel
CN Quievita
CN Relaminal
CN Relanium
CN Ro 5-2807
CN Saromet
CN Seduxen
CN Setonil
CN Sibazon
CN Sibazone
CN Sonacon
CN Stesolid
CN Stesolin
CN Tranimul
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
FS 3D CONCORD
DR 11100-37-1, 53320-84-6
MF C16 H13 Cl N2 O
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGPAT, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, TOXLIT, TULSA, ULIDAT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11060 REFERENCES IN FILE CA (1967 TO DATE)
56 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
11070 REFERENCES IN FILE CAPLUS (1967 TO DATE)
55 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> file embase biosis medline caplus uspatfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	6.22	6.37

FILE 'EMBASE' ENTERED AT 17:05:30 ON 13 FEB 2002
COPYRIGHT (C) 2002 Elsevier Science B.V. All rights reserved.

FILE 'BIOSIS' ENTERED AT 17:05:30 ON 13 FEB 2002
COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'MEDLINE' ENTERED AT 17:05:30 ON 13 FEB 2002

FILE 'CAPLUS' ENTERED AT 17:05:30 ON 13 FEB 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATFULL' ENTERED AT 17:05:30 ON 13 FEB 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

=> s 439-14-5/rn or diazepam
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L2 95183 439-14-5/RN OR DIAZEPAM

=> s epilepsy or epileptic seizure or seizure
L3 264445 EPILEPSY OR EPILEPTIC SEIZURE OR SEIZURE

=> s l2 and l3
L4 9948 L2 AND L3

=> s epileptic seizure
L5 11085 EPILEPTIC SEIZURE

=> s l2 and l5
L6 337 L2 AND L5

=> s l6 and py<2000

```
   2 FILES SEARCHED...
   4 FILES SEARCHED...
L7          298 L6 AND PY<2000

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8           247 DUP REM L7 (51 DUPLICATES REMOVED)

=> s oil formulation
L9         2406 OIL FORMULATION

=> s l9 or lipiophilic
L10        2407 L9 OR LIPIOPHILIC

=> s l10 and l8
L11           0 L10 AND L8

=> s l10 and l6
L12           0 L10 AND L6

=> s l8 and py<1999
   1 FILES SEARCHED...
   2 FILES SEARCHED...
L13         230 L8 AND PY<1999

=> s lipophilic or lipid or fat or oil
L14     2521549 LIPOPHILIC OR LIPID OR FAT OR OIL

=> s l13 andl 14
MISSING OPERATOR L13 ANDL
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l13 and l14
L15          31 L13 AND L14

=> dup rem l5
PROCESSING IS APPROXIMATELY   9% COMPLETE FOR
<------User Break------>
u
=> dup rem l15
PROCESSING COMPL5  LETED FOR L15
L16          31 DUP REM L15 (0 DUPLICATES REMOVED)

=> d l16 1-31 ab bib kwic

L16  ANSWER 1 OF 31  USPATFULL
AB      The present invention provides methods for detecting the presence of or
        determining the amount of a ligand in a fluid sample. The methods
        comprise providing a first reagent comprising a sol particle having a
        detectable physical property bound to the ligand or ligand analogue (in
        a competitive format) or a substance capable of specifically coupling
        with the ligand (in a sandwich format), providing a second reagent
        having a detectable physical property comprising a sol particle bound
to
        a substance capable of specifically coupling with the ligand and/or
        ligand analogue, if present, combining the first reagent, second
reagent
        and the fluid sample and detecting before, during or after the
reaction,
```

a change in the physical property of the sol particles, which provides a
qualitative or quantitative indication of the ligand in the fluid sample. The reagents couple with one another as a function of the presence of the ligand in the sample to thereby produce a change in the physical property of the sol particles which is related to the degree of
coupling of the reagents. The invention also provides a kit for detecting the presence of or determining the amount of a ligand in a fluid sample. The invention further provides immunological complexes having a detectable physical property.

AN 1998:159711 USPATFULL
TI Homogeneous sol-sol assay
IN Hunter, Thomas J., Cooper City, FL, United States
Pfadenhauer, Ernest H., Costa Mesa, CA, United States
PA Dade Behring Inc., Deerfield, IL, United States (U.S. corporation)
PI US 5851777 19981222 <--
AI US 1996-596825 19960205 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Caputa, Anthony C.; Assistant Examiner: Navarro, Mark
LREP Lowen, Cara Z.
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1828
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5851777 19981222 <--

SUMM . . . one analyte or ligand in a sample. For example, concurrent administration of anticonvulsant drugs is used in the management of **epileptic seizures**. (G. Moriarty, Clinical Chemistry, eds. L. Kaplan and A. Pesce, 605-606 (1989)). Therefore, it would be useful to have an. . .

SUMM . . . second polymer. In a preferred method, the first protein comprises rabbit gamma globulin. Preferably, the blocking agent is selected from non-**fat** dry milk or casein.

DETD . . . known in the art and include proteins, detergents, as well as polymers such as PEG and PVP. For gold sols, non-**fat** dry milk and casein are the preferred blocking agents, with casein most preferred. Stabilization can be monitored by resistance to. . .

DETD . . . whole serum to which this assay would be applicable: acetaminophen, N-acetylprocainamide, amikacin, amitriptyline, amobarbital, butabarbital, caffeine, carbamazepine, cocaine, codeine, cortisol, **diazepam**, digitoxin, digoxin, ethosuximide, gentamicin, glutethimide, hexobarbital, ibuprofen, kanamycin, lidocaine, methsuximide, morphine, netilmicin, nortriptyline, oxycodone, pentobarbital, phencyclidine phenobarbital, phenytoin, primidone, procainamide,. . .

DETD . . . diluted to 90 mL with purified water, added to the pH adjusted gold sol, and stirred well for 30 minutes. Non-**fat** dry milk (CARNATION.RTM.) was added such that the final concentration of milk was 0.04%. The mixture was stirred overnight at. . .

DETD . . . diluted to 9.0 mL with purified water, added to the pH adjusted gold sol, and stirred well for 60 minutes. Non-**fat** dry milk (Carnation) was added such that the final concentration of milk was 0.04% and the mixture was stirred overnight. . .

DETD . . . diluted to 90 mL with purified water, added to the pH adjusted

gold sol, and stirred well for 30 minutes. Non-**fat** dry milk (Carnation) is added such that the final concentration of milk was 0.04%. The mixture is stirred overnight at. . .

DETD . . . diluted to 9.0 mL with purified water, added to the pH adjusted gold sol, and stirred well for 60 minutes. Non-**fat** dry milk (Carnation) is added such that the final concentration of milk is 0.04% and the mixture is stirred overnight. . .

DETD . . . diluted to 90 mL with purified water, added to the pH adjusted gold sol, and stirred well for 30 minutes. Non-**fat** dry milk (Carnation) is added such that the final concentration of milk was 0.04% The mixture is stirred overnight at. . .

DETD . . . diluted to 9.0 mL with purified water, added to the pH adjusted gold sol, and stirred well for 60 minutes. Non-**fat** dry milk (Carnation) is added such that the final concentration of milk is 0.04% and the mixture was stirred overnight. . .

L16 ANSWER 2 OF 31 USPATFULL

AB This invention discloses that kainic acid receptor antagonists (KA antagonists) can act as "safener" agents to reduce or prevent adverse side effects caused by NMDA antagonists. NMDA antagonists can reduce excitotoxic brain damage due to stroke, cardiac arrest, asphyxia, etc., but they also cause toxic damage to certain types of neurons, as well as psychotomimetic effects such as hallucinations. Co-administration of a KA antagonist can (1) reduce or prevent such undesired side effects, and (2) increase the extent of neuronal protection provided to the CNS, beyond the levels of protection that can be provided by NMDA antagonists alone, or non-NMDA antagonists alone. Therefore, co-administration of a KA antagonist allows NMDA antagonists to be used more safely and effectively.

AN 1998:69048 USPATFULL

TI Use of kainic acid antagonists to prevent toxic side effects of NMDA antagonists

IN Olney, John W., 1 Lorenzo La., St. Louis, MO, United States 63124

PI US 5767130 19980616 <--

AI US 1995-407068 19950320 (8)

RLI Continuation-in-part of Ser. No. US 1992-877839, filed on 1 May 1992 which is a continuation-in-part of Ser. No. US 1990-467139, filed on 18 Jan 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-424548, filed on 20 Oct 1989, now patented, Pat. No. US 5034400

DT Utility

FS Granted

EXNAM Primary Examiner: Weddington, Kevin E.

LREP Kelly, Patrick D.

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 1795

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5767130 19980616 <--

SUMM . . . food poisoning which involve an excitotoxic poison such as domoic acid, and seizure-mediated neuronal degeneration, which can result from persistent **epileptic seizure** activity (status epilepticus). A large body of evidence has implicated the NMDA receptor as the receptor subtype through which Glu. . .

SUMM (3) **diazepam** (marketed under the trade name VALIUM), a drug in the benzodiazepine class, confers partial protection against NMDA antagonist neurotoxicity (Olney. . . receptor) is considered a component part of the GABAA receptor complex. Therefore, it has been postulated that the action of **diazepam** in protecting against NMDA antagonist neurotoxicity is due to its influence on GABA.sub.A receptor activity. The observation that **diazepam** provides only partial protection (in contrast to more complete protection by barbiturates) may relate to the fact that **diazepam** does not, like barbiturates, act as a direct GABA agonist even in the absence of GABA; rather, the action of **diazepam** is dependent upon GABA being present and is limited to potentiating the action of GABA.

DETD . . . alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, gelatin, syrup, methyl cellulose, methyl- and propyl- hydroxybenzoates, talc, magnesium, stearate, water, mineral **oil**, and the like. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents. . .

L16 ANSWER 3 OF 31 USPATFULL

AB The present invention provides methods for treating migraine headache. The methods useful according to the invention involve the treatment of patients who experience symptoms of migraine headache with compounds that directly or indirectly activate GABA.sub.A receptors.

AN 1998:69035 USPATFULL

TI Method for treating vascular headaches

IN Moskowitz, Michael A., Belmont, MA, United States

PA The General Hospital Corporation, Boston, MA, United States (U.S. corporation)

PI US 5767117 19980616 <--

AI US 1994-342090 19941118 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Spivack, Phyllis G.

LREP Wolf, Greenfield & Sacks, P.C.

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 5 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 783

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5767117 19980616 <--

SUMM . . . binding site of GABA.sub.A that modulates GABA.sub.A receptor activity. The preferred benzodiazepine agonists are FG8205, bretazenil, divaplon, alpidem, abecarnil, alprazolam, **diazepam**, and flunitrazepam.

DETD . . . treated with drugs useful according to the methods of the invention, including patients who are not epileptics undergoing treatment for **epileptic seizures**, who are not women being treated for premenstrual syndrome or who are not women using oral contraceptive agents. In other. . .

DETD . . . peripheral receptors. For instance clonazepam is more potent at

central than peripheral receptors by a few thousand times. Others, like **diazepam**, have roughly equal potencies at both.

DETD . . . the GABA.sub.A receptor and are useful in treating migraine include clonazepam, FG8205, bretazenil (Ro166028); divaplon (RU32698); alpidem; abecarnil (ZK11219); alprazolam; **diazepam**; zolpidem; flunitrazepam; Ro54864:
7-chloro-1,3-dihydro-1-methyl-5-(p-chlorophenyl)-
2H-1,4-benzodiazepine-2-one; PK8165:
phenyl-2[(piperidinyl-4)-2-ethyl]-4-

quinoline; PK9084: phenyl-2[(piperidinyl-3)-2-ethyl]-4-quinoline; and PK11195: 1-(2-chlorophenyl)-N-methyl-N-(1-methyl-propyl)-3-isoquinalinecarboxamide. The chemical structures of some of the compounds are. . .

DETD . . . humans for purposes other than the treatment of migraine. These compounds include THIP, tiagabine, FG8205, bretazenil, divaplon, alpidem, abecarnil, alprazolam, **diazepam**, and flunitrazepam.

DETD . . . Other procedures for decreasing the penetrability of the compound into the brain involve increasing the molecular weight or decreasing the **lipid** partition coefficient. Those of ordinary skill in the art will know other mechanisms for modifying molecules to prevent their passage. . .

DETD . . . the art. They include polymer based systems such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer systems that are **lipids** including sterols such as cholesterol, cholesterol esters and fatty acids or neutral **fats** such as mono-, di- and triglycerides; hydrogel release systems; silastic systems; peptide based systems; wax coatings, compressed tablets using conventional. . .

CLM What is claimed is:

6. The method of claim 2, wherein the benzodiazepine is **diazepam**.

8. The method of claim 1, wherein the agonist that binds to the benzodiazepine binding site of the GABA.sub.A receptor is selected from the group consisting of clonazepam; FG8205; bretazenil (Ro166028); divaplon (RU32698); alpidem; abecarnil (ZK11219); alprazolam; **diazepam**; zolpidem and flunitrazepam [; Ro54864:7-chloro-1,3-dihydro-1-methyl-5-(p-chlorophenyl) -2H-1, 4-benzodiazepine-2-one; PK8165; phenyl-2[(piperidinyl4)-2-ethyl]4-quinoline; PK0984; phenyl-2[piperidinyl-3)-2-ethyl]-4-quinoline; and PK11195:1-(2-chlorophenyl)-N-methyl-N-(1-methyl-propyl)-3-isoquinalinecarboxamide].

IT 57-83-0, Progesterone, biological studies 128-20-1, 3.alpha.-Hydroxy-5.beta.-pregnan-20-one **439-14-5**, Diazepam 498-94-2, Isonipecotic acid 498-95-3, Nipecotic acid 498-96-4, Guvacine 516-54-1, 3.alpha.-Hydroxy-5.alpha.-pregnan-20-one 566-58-5 645-65-8, Imidazole-4-acetic acid 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 12794-10-4D, Benzodiazepine, derivs. 14439-61-3 28981-97-7, Alprazolam 29676-71-9 53602-00-9, 4,5,6,7-Tetrahydroisoxazolo[4,5-c]pyridin-3-ol 60643-86-9, Vigabatrin 62665-96-7 64603-90-3, Isoguvacine 64603-91-4, 4,5,6,7-Tetrahydroisoxazolo[5,4-c]pyridin-3-ol 71376-02-8 72241-46-4, Dihydromuscimol 72450-62-5, Piperidine-4-sulfonic acid 77472-98-1, PK8165 77472-99-2, PK9084 82626-01-5, Alpidem 84379-13-5, Bretazenil 85532-75-8, PK11195 90808-12-1, Divaplon 92138-10-8 95596-29-5 97164-95-9 110283-66-4, CI-966 111841-85-1, Abecarnil 115103-54-3, Tiagabine 122384-14-9, FG8205 132033-96-6 179261-24-6 179393-58-9, SKF 89975A
(GABAA receptor activators for treating vascular headaches)

L16 ANSWER 4 OF 31 USPATFULL

AB A water-dispersible tablet comprises an active compound such as acyclovir or lamotrigine and a dispersing agent. The dispersing agent is a swellable clay such as a smectite, e.g. Veegum F or bentonite, and is generally present within the granules of the tablet to provide a tablet which is capable of dispersing in water within 3 minutes to provide a dispersion which will pass through a 710 .mu.m sieve. The tablet can be

optionally film-coated in which case the dispersion time is less than 5 minutes.

AN 97:117723 USPATFULL

TI Water-dispersible tablets

IN Fielden, Krystyna Elzbieta, Dartford, United Kingdom

PA Glaxo Wellcome Inc., Research Triangle Park, NC, United States (U.S. corporation)

PI US 5698226 19971216 <--

AI US 1996-659316 19960606 (8)

RLI Division of Ser. No. US 1993-90111, filed on 13 Jul 1993, now patented, Pat. No. US 5556639

DT Utility

FS Granted

EXNAM Primary Examiner: Venkat, Jyothsan

LREP Nixon & Vanderhye

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1595

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5698226 19971216 <--

DETD . . . which can be treated by them (incorporated by reference): acyclovir (UK No.1523865), lamotrigine (EP Nos. 021 121 and 247 829), **diazepam**, paracetamol, (both commercially available), 1-(.beta.-D-arabinofuranosyl)-5-propy-1-ynyl-uracil (EP No. 0272 065), 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone (EP No. 0123 238), allopurinol (G.B. 1445 983).

DETD . . . 75% w/w

2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone - 50 to 85% w/w, preferably 60 to 75% w/w

Allopurinol - 25 to 80% w/w, preferably 45 to 65% w/w

Diazepam - 4 to 30% w/w, preferably 8 to 16% w/w

Pseudoephedrine - 5 to 50% w/w, preferably 15 to 30% w/w

Dextromethorphan. . .

DETD . . . to 5% w/w, preferably 1 to 3% w/w, zinc stearate 0.01 to 2% w/w, 0.5 to 1.5% w/w, hydrogenated vegetable **oil** 0.5 to 5% w/w, preferably 1 to 3% w/w. More suitably the lower value is 0.25%.

DETD . . . in human medicine in the treatment of disorders of the central nervous system and in particular in the treatment of **epileptic seizures**. They may be administered one or more times per day, for example up to five times per day, at the. . . disorder being treated, the unit dose adopted and the total dose required. A suitable daily dose for the treatment of **epileptic seizures** will generally lie in the range of 5 to 500 mg., more often in the range of 25 to 400. . .

DETD . . . for each Example is as follows:

Example 41 1(D-arabinofuranosyl)-5-propynyluracil

Example 42 Allopurinol

Example 43 2[4(4-chlorophenyl)cyclohexyl3-hydroxy-1,4,napthoquinone

Example 44 Paracetamol

Example 45 **Diazepam**

IT 90-82-4 93-14-1, Guaiphenesin 103-90-2, Paracetamol 125-28-0, Dihydrocodeine 125-71-3 290-38-0D, 1,2,4-Triazine, derivs. 315-30-0, Allopurinol **439-14-5**, Diazepam 486-12-4, Triprolidine 723-46-6 738-70-5 1318-93-0, Montmorillonite, uses 2465-59-0 12174-11-7, Attapulgite 12679-43-5D, Naphthalenedione, derivs. 30516-87-1 39809-25-1 59277-89-3, Acyclovir 77181-69-2 84057-84-1, Lamotrigine 84558-93-0 87848-99-5, Acrivastine 94015-53-9 104227-87-4 119644-22-3 124832-26-4 130450-97-4

130721-33-4
(water-dispersible tablets contg.)

L16 ANSWER 5 OF 31 USPATFULL
AB A method for administering a therapeutically effective amount of a biologically active substance to the circulatory system of a mammal including administering a pharmaceutical composition having a total volume of 1-1000 .mu.l to a nasal mucosal membrane of the mammal, the pharmaceutical composition including the therapeutically effective amount of the biologically active substance dissolved or suspended in a volume of 1-1000 .mu.l of an n-ethylene glycol containing vehicle including at least one n-ethylene glycol represented by the formula:

H(OCH.sub.2 CH.sub.2).sub.p OH

wherein p is from 1 to 8, so that upon administration of the pharmaceutical composition to the nasal mucosal membrane, absorption of the biologically active substance through the mucosal membrane and into the blood stream of the mammal rapidly takes place and thereby allows the biologically active substance to exert its therapeutic effect.
AN 97:112440 USPATFULL
TI Method of administering a biologically active substance
IN Bechgaard, Erik, Hellerup, Denmark
Gizurarson, Sveinbjorn, Keflavik, Iceland
Hjortkj.ae butted.r, Rolf Kuhlman, Humleb.ae butted.r, Denmark
PA Bechgaard International Research and Development A/S, Hellerup, Denmark (non-U.S. corporation)
PI US 5693608 19971202 <--
AI US 1995-395838 19950228 (8)
RLI Continuation of Ser. No. US 1993-151802, filed on 15 Nov 1993, now patented, Pat. No. US 5428006 which is a continuation of Ser. No. US 1993-71604, filed on 4 Jun 1993, now abandoned which is a continuation of Ser. No. US 1992-870893, filed on 20 Apr 1992, now abandoned which is
a division of Ser. No. US 1991-696564, filed on 8 May 1991, now abandoned
PRAI DK 1990-1170 19900510
DK 1990-2075 19900830
DT Utility
FS Granted
EXNAM Primary Examiner: Davenport, Avis M.
LREP Evenson, McKeown, Edwards & Lenahan P.L.L.C.
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN 16 Drawing Figure(s); 16 Drawing Page(s)
LN.CNT 1823
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5693608 19971202 <--
SUMM . . . must be biocompatible with mucus and hence have a certain degree of hydrophilicity. However, the vehicle should preferably also posses **lipophilic** properties in order to dissolve a physiologically active amount of certain biologically active substances.
SUMM Lau and Slattery (1989) studied the absorption characteristics of **diazepam** and lorazepam following intranasal administration for the treatment of status epilepticus. In order to solubilize these drugs,
a non-ionic surfactant, polyoxyethylated castor **oil**, was selected as the least irritating out of several solvents studied including polyethyleneglycol 400. **Diazepam** absorption was 84

and 72%, respectively, in two adults measured over a period of 60 hours.

However, the peak concentration. . . peak (2.3 hours). The authors conclude that the intranasal route of administration had limited potential for the acute treatment of **epileptic seizures.**

SUMM International Patent Publication No. WO 86/04233 discloses a pharmaceutical composition wherein the drug (e.g. **diazepam**) is dissolved in a mixture of propellant and co-solvent e.g. glycerolphosphatide. This composition requires a pressurized system and at least. . .

SUMM wherein p is an integer of 3-8 or in water or in a vegetable **oil** or in a mixture of water and/or n-ethylene glycol and/or vegetable **oil.**

SUMM . . . anti-emetica having a regulatory effect on the motility of the intestine such as domperidon; Anti-epileptica and anti-spasmolytica such

as clonazepam, **diazepam**, nitrazepam, lorazepam etc.; Anti-histaminic and histaminic agents such as diphenhydramin HCl, chloropheniramine maleate, clemastine, histamine, prophenpyridamine maleate, chlorprophenpyridamine maleate, disodium. . . citrate, or .alpha..sub.1 -antitrypsin etc.; Sedatives such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ehtyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. . . and synthetic modifications thereof etc.; Tranquillisers such as alprozolam,

bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. . .

SUMM . . . derivatives and analogues thereof and tranquilizer such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. .

SUMM . . . invention, the active substance is selected among antiepileptica, spasmolytics and tranquilizers selected from the group of benzodiazepines such as clonazepam, **diazepam**, flunitrazepam, triazolamn, lorazepam, nitrazepam or mixtures thereof.

SUMM . . . in addition to the biologically active substance(s). Such carrier may comprise water and/or n-ethylene glycol and/or propylene glycol and/or vegetable **oil** and/or even powdery carrier of e.g. microspheres.

SUMM . . . minor proportions of one or more compound(s) selected from the group consisting of surfactants, absorption promoters, water absorbing polymers, microspheres, **oils**, emulsions, liposomes, substances that inhibit enzymatic degradation, alcohols, organic solvents, water, hydrophobic agents, pH-controlling agents, preservatives and osmotic pressure controlling. . .

SUMM wherein p is 3 to 8 or in water or in a vegetable **oil** or in a

mixture of water and/or n-ethylene glycol and/or vegetable **oil** .

SUMM wherein p is 3 to 8 or in water or in a vegetable **oil** or in a mixture of water and/or n-ethylene glycol and/or vegetable **oil** for application to a mucosal membrane.

SUMM . . . [9004 76-6]). Glycofurol 75 is a colourless liquid miscible with water, alcohols, such as methanol, ethanol, n-proypanol, glycerol and various **oils** in all proportions and has a b.p. about 155.degree. C. GF is reported to cause irritation when used in compositions. . .

SUMM . . . relevant dose for human subjects in only e.g. 25-300 .mu.l of the vehicle. In aqueous solutions clinically relevant doses of **diazepam** and clonazepam will alternatively have to be dissolved in about 5000 ml and >10 ml, respectively.

SUMM The vehicle system according to the invention may be used in combination with various co-solvents, such as vegetable **oil** such as Miglyol.RTM. 840 (Dynamit Nobel Chemie, Troisdorf, W-Germany) or optionally hydrogenated or ethoxylated castor **oil**, which surprisingly increases the possibilities for designing a controlled release--formulation such as a **diazepam** formulation which avoids peak plasma concentrations.

SUMM . . . according to the invention may comprise one or more additional pharmaceutical exipients, such as: surfactants and absorption promoters having a hydrophillic-**lipophilic** balance from about 6 to 26 and ionic as well as non-ionic surfactants including polyoxyethylene alcohol ethers, bile salts and. . . aprotinin; Alcohols, such as, ethanol, glycerol, or benzylalcohol; Organic solvents, such as, ethylacetate, or benzylalcohol; Hydrophobic agents, such as vegetabile **oil**, e.g. soybean **oil**, peanut **oil**, coconut **oil**, corn **oil**, olive **oil**, sunflower **oil**, castor **oil**, Miglyol.RTM. 810/812/840 or mixtures thereof; pH-controlling agents, such as, nitric acid, phosphoric acid, or acetic acid, citrate: Preservatives and osmotic. . .

DRWD FIG. 6 shows a graphical representation showing the mean plasma level of **diazepam** after administration of preparations comprising glyycofuryol and various co-solvents,

DETD . . . .mu.l F in PEG 1

22 f

23

24

25 m

26

27 5 30 .mu.l F in PEG + GF 1

28 f

29

30

Abbreviations: D = **Diazepam** 3%; L = Lorazepam 5%; F = Flunitrazepam 1%; PEG = Polyethylene glycol 200; GF = Glycofurol 75; PEG +. . .

DETD 3 mg **diazepam** in 100 .mu.l vehicle was prepared and applied to rabbits in a manner analogous to that described in example 6. The following vehicles were used: (1) Glycofurolum 75 (GF); (2) Miglyol 840+GF (7+3) and (3) Vegetable **oil**+GF (7+3). Blood samples were obtained from the marginal ear vein at following time intervals:

0,

5, 10, 15, 30 and 60 minutes and the **diazepam** concentration was determined by HPLC.

DETD FIG. 6 shows the mean plasma **diazepam** concentrations obtained after the intranasal administration. An initial peak plasma concentration can be controlled dependent on the GF/**oil** vehicle used. The plasma concentration for the GF formulation at 5 minutes is about 55% of an intravenous injection of 3 mg **diazepam** as Stesolid.RTM. (Dumex A/S, Denmark).

DETD Surprisingly it has been found that the intranasal absorption of e.g. benzodiazepines, such as clonazepam and **diazepam**, in the vehicles according to the invention is very similar to an intravenous injection (i.v.). From FIG. 1 it appears. . .

DETD . . . volume is desirable in order to reduce or eliminate a local irritating effect. Alternatively a non irritating co-solvent, e.g. vegetabile **oil**, may be added. In this way a desired dose volume or delivery rate may also be obtained. To reduce plasma. . .

DETD TABLE 2

THE INFLUENCE OF GLYCOFUROLE (% GF) IN TETRAETHYLENEGLYCOL (4EG) AND VEGETABILE **OIL** (OV) IN GF ON THE TIME TO RESPONSE (minutes) AFTER INTRANASAL APPLICATION OF 0.25 mg CLONAZEPAM TO RABBITS (n = 4).

NOTICE:. . .

DETD Lau, S. W. J. and Slattery, J. T. (1989), "Absorption of **diazepam** and lorazepam following intranasal administration." Inernational Journal of Pharmaceutics, 54, 171-174.

CLM What is claimed is:

19. The method according to claim 1 wherein the vehicle further comprises a vegetable **oil**.

IT 50-56-6, Oxytocin, biological studies 50-57-7, Lypressin 146-22-5, Nitrazepam **439-14-5**, Diazepam 846-49-1, Lorazepam 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 9001-25-6, Blood coagulation factor VII 9001-27-8, Blood coagulation factor VIII 9001-28-9, Blood coagulation factor IX 9002-67-9, LH 9002-68-0, FSH 9002-72-6, Growth hormone 9004-10-8, Insulin, biological studies 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9034-40-6, LHRH 11000-17-2, Vasopressin 16679-58-6, DDAVP 28911-01-5, Triazolam 50647-00-2, LTH 58822-25-6, Leucine enkephalin 63631-40-3, DADLE 66960-34-7, Metkephamid
(pharmaceutical intranasal formulation contg.)

L16 ANSWER 6 OF 31 USPATFULL

AB A method is disclosed for reducing excitotoxic damage to neurons, which can occur as a result of stroke, cardiac arrest, or other events or conditions. This method involves administering an aminoglycoside that suppresses the flow of calcium ions into neurons through N-type calcium channels. To be effective for such use, an aminoglycoside must suppress N-channel activity at a potency greater than streptomycin. Aminoglycosides which meet this criterion (which includes neomycin and Gentamicin) can suppress the depolarizing activation of neurons, which in turn controls the release of glutamate, a neurotransmitter that becomes an endogenous toxin under excitotoxic conditions. Numerous aminoglycosides were tested in in vitro screening tests using brain cell membrane fragments to evaluate N-channel blocking potency. Aminoglycosides with the highest N-channel blocking potency were then tested using (1) in vitro tests on hippocampal brain tissue, to evaluate recovery of neuronal activity after a period of oxygen deprivation; (2) in vivo tests to evaluate the control of induced seizures in intact

adult mammals; and (3) in vivo tests to evaluate the reduction of brain damage due to surgically-induced ischemia in intact adult mammals. The results showed that (1) aminoglycosides which are more potent than streptomycin in blocking N-channel ion flow are effective in reducing excitotoxic brain damage, without causing undesired side effects, and (2) the effectiveness of all BBB-permeable aminoglycosides tested to date in preventing excitotoxic brain damage is directly correlated with their potency in suppressing N-channel activity. Evaluation of chemical structures also indicates a correlation between the number of primary amino groups on an aminoglycoside, and its potency as an N-channel blocker and neuroprotective agent.

AN 97:94221 USPATFULL

TI Use of aminoglycosides to protect against excitotoxic neuron damage

IN Marangos, Paul J., Encinitas, CA, United States

PA Cypros Pharmaceutical Corporation, Carlsbad, CA, United States (U.S. corporation)

PI US 5677288 19971014 <--

AI US 1994-228229 19940415 (8)

RLI Continuation-in-part of Ser. No. US 1992-855600, filed on 20 Mar 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-700765, filed on 15 May 1991, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Peselev, Elli

LREP Kelly, Patrick D.

CLMN Number of Claims: 15

ECL Exemplary Claim: 1

DRWN 8 Drawing Figure(s); 8 Drawing Page(s)

LN.CNT 1695

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5677288 19971014 <--

SUMM . . . any molecule, and it also promotes the release of iron ions from ferritin, which in turn promotes a process called "**lipid** peroxidation" which destroys cell membranes.

SUMM . . . such as stroke or cardiac arrest, and to other events or conditions that cause excitotoxic damage to neurons, such as **epileptic seizures** and possibly some types of progressive neurodegenerative diseases.

SUMM . . . or after a stroke or cardiac arrest) or as a result of various other events or conditions such as an **epileptic seizure** or certain types of poisoning. This method involves the administration of a therapeutically effective amount of an aminoglycoside which suppresses. . .

DETD . . . during or after a stroke, cardiac arrest, or heart attack) or during various other events or conditions such as an **epileptic seizure** or certain types of poisoning or neurodegenerative diseases which have excitotoxic components. This method involves administering, to a patient suffering. . .

DETD . . . damage induced by convulsant drugs or electroshock treatment. These tests showed that aminoglycosides can provide comparable or better protection than **diazepam** (widely sold and used under the trademark VALIUM), an anxiolytic drug that is widely used in research as an anti-convulsant drug, without causing the animals to display the undesired behavioral side effects associated with **diazepam**.

DETD . . . Animals seizures side-effects

ICV administration			
Saline	9	89%	-

Neomycin (60 ug)			
	5	40%	-
Neomycin (120 ug)			
	5	20%	-
IP administration			
Saline	8	100%	-
Diazepam (2 mg/kg)			
	4	75%	++
Neomycin (10 mg/kg)			
	5	60%	-
Neomycin (45 mg/kg)			
	4	0%	-
Neomycin (90 mg/kg)			
	5	40%	-

DETD . . .	# of Animals	Seizure Score	Effects
Saline	14	1.8	-
40 ug Neomycin			
	13	4.1	-
40 ug Gentamicin			
	8	4.9	-
5 ug **Diazepam**			
	13	4.4	+

DETD . . . show that both of the aminglycosides tested were able to inhibit electrically-induced seizures in a manner similar to that of **diazepam**, but with fewer behavioral effects.

L16 ANSWER 7 OF 31 USPATFULL

AB This invention discloses that ibogaine, a plant derivative, can be used as a safe NMDA antagonist at relatively high dosages (including dosages high enough to cause hallucinations), to reduce or prevent excitotoxic brain damage due to stroke, cardiac arrest, trauma or other forms of neuronal injury or degeneration, without causing the neurotoxic side effects caused by other NMDA antagonist drugs. The relative safety of ibogaine is due to antagonist activity at neuronal sigma receptors, which had not been known prior to discovery by the Applicant. This invention also discloses that ibogaine also can be administered in combination with (1) drugs that suppress activity at muscarinic acetylcholine receptors, or (2) drugs which suppress activity at the kainic acid subclass of glutamate receptors, to reduce or avoid the hallucinatory effects of ibogaine and provide a higher level of neuroprotective activity.

AN 97:40786 USPATFULL

TI Use of ibogaine in reducing excitotoxic brain damage

IN Olney, John W., 1 Lorenzo La., St. Louis, MO, United States 63124

PI US 5629307 19970513 <--

AI US 1995-398731 19950306 (8)

RLI Continuation-in-part of Ser. No. US 1992-877839, filed on 1 May 1992 which is a continuation-in-part of Ser. No. US 1990-467139, filed on 18 Jan 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-424548, filed on 20 Oct 1989, now patented, Pat. No. US 5034400

DT Utility

FS Granted

EXNAM Primary Examiner: Weddington, Kevin E.

LREP Kelly, Patrick D.

CLMN Number of Claims: 5

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1250
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5629307 19970513 <--
SUMM . . . et al 1991; Trujillo and Akil 1991; Ben-Eliyahu et al 1992; Tal
and Bennett 1993), to benzodiazepine anxiolytics such as **diazepam** (sold under the trade name VALIUM; Turski et al, PCT patent application WO 94/01094), to cocaine (Pudiak and Bozarth 1993),. . .
SUMM . . . food poisoning which involve an excitotoxic poison such as domoic acid, and seizure-mediated neuronal degeneration, which can result from persistent **epileptic seizure** activity (status epilepticus). A large body of evidence has implicated the NMDA receptor as one receptor subtype through which Glu. . .
DETD . . . poisoning which involve an excitotoxic poison such as domoic acid, and seizure-mediated neuronal degeneration, which includes several
types of severe **epileptic seizures**. As an NMDA antagonist which does not cause toxic side effects, ibogaine is a good candidate drug for protecting neurons. . .
DETD . . . phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoates, talc, magnesium, stearate, water, mineral **oil**, and the like. The formulations can additionally include lubricating agents, wetting agents, emulsifying
and suspending agents, preserving agents, sweetening agents. . .

L16 ANSWER 8 OF 31 USPATFULL
AB Methods and compositions are disclosed for treating or preventing adverse CNS effects produced by NMDA receptor hypofunction (NRH), including hypofunction induced by NMDA antagonist drugs, and hypofunction occurring as a causative or aggravating factor in schizophrenia. One method of this invention comprises administering an alpha-2 adrenergic (.alpha.2) receptor agonist drug along with an NMDA antagonist drug. The NMDA antagonist drug exerts a primary benefit in reducing excitotoxic brain damage, alleviating neuropathic pain, or preventing or avoiding tolerance or addiction to various types of drugs.
The .alpha.2 agonist drug acts as a secondary or "safener" drug, to prevent the neurotoxic side effects that would be caused by the NMDA antagonist in the absence of the safener drug. Another method disclosed herein involves the use of an .alpha.2 agonist drug, by itself, to combat a different and naturally-occurring form of NMDA receptor hypofunction which occurs as a causative or aggravating mechanism in people suffering from schizophrenia. Although .alpha.2 agonists are usually not effective in treating long-standing cases of chronic schizophrenia, where pathological changes in the brain have already reached or approached maximal levels, .alpha.2 agonists can be administered early in the illness, such as at the first signs of schizophrenic illness, and continuously or intermittently thereafter to prevent the development or worsening of pathological brain changes.
AN 97:16066 USPATFULL
TI Use of alpha-2 adrenergic drugs to prevent adverse effects of NMDA receptor hypofunction (NRH)
IN Olney, John W., Ladue, MO, United States
Farber, Nuri B., University City, MO, United States
PA Washington University, St. Louis, MO, United States (U.S. corporation)
PI US 5605911 19970225 <--

AI US 1995-381334 19950131 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Kelly, Patrick D.
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1935
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5605911 19970225 <--
SUMM . . . disorders. In an acute crisis such as a stroke or CNS trauma, and in certain other events such as severe **epileptic seizures**, the cellular transport mechanism that removes glutamate almost immediately from the synaptic fluid, and pumps it back inside a neuron. . .
SUMM . . . poisoning which involve an excitotoxic poison such as domoic acid, and seizure-mediated neuronal degeneration, which includes several types of severe **epileptic seizures**. NMDA antagonists can help to protect neurons in the CNS against such damage (e.g., Olney 1990; Choi 1992), and a. . .
SUMM . . . of barbiturates, such as secobarbitol, which are called "direct GABA agonists" (Olney et al 1991). Unlike benzodiazepine drugs such as **diazepam** (sold under the trademark VALIUM), which can only increase the effects of naturally occurring inhibitory neurotransmitter called gamma-amino-butyric acid (GABA),. . .
DETD . . . prevention of neuronal degeneration associated with acute CNS injury syndromes, including hypoxia/ischemia (stroke), cardiac arrest, asphyxia, CNS trauma, and major **epileptic seizures**; (2) prevention of gradual excitotoxic neuronal degeneration which may accompany various progressive degenerative diseases, such as Alzheimer's disease, amyotrophic lateral. . .
DETD . . . phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, gelatin, syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium, stearate, water, mineral **oil**, and the like. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents. . .
CLM What is claimed is:
. . . and the alpha-2 adrenergic agonist drug are co-administered to the patient in order to reduce excitotoxic brain damage caused by **epileptic seizures**.

L16 ANSWER 9 OF 31 USPATFULL
AB Method, compositions, and compounds for modulating brain excitability to alleviate stress, anxiety, insomnia and seizure activity using certain steroid derivatives that act at a newly identified site on the gamma-aminobutyric acid receptor-chloride ionophore (GR) complex.
AN 97:1455 USPATFULL
TI Methods, compositions, and compounds for allosteric modulation of the gaba receptor by members of the androstane and pregnane series
IN Bolger, Michael B., Los Alamitos, CA, United States
Gee, Kelvin W., Irvine, CA, United States
Lan, Nancy C., South Pasadena, CA, United States

Purdy, Robert H., La Jolla, CA, United States
Mirsadeghi, Seid, Rolling Hills, CA, United States
Tahir, Syed Hasan, Edmonton, Canada
Belelli, Delia, Kingsbarns by St. Andrews, Scotland

PA University of Southern California, Los Angeles, CA, United States (U.S. corporation)

PI US 5591733 19970107 <--

AI US 1993-101497 19930802 (8)

DCD 20100803

RLI Continuation of Ser. No. US 1991-745216, filed on 13 Aug 1991, now patented, Pat. No. US 5232917 which is a continuation-in-part of Ser. No. US 1990-521724, filed on 10 May 1990, now patented, Pat. No. US 5120723 which is a continuation-in-part of Ser. No. US 1989-379047, filed on 13 Jul 1989, now abandoned which is a continuation-in-part of Ser. No. US 1987-89362, filed on 25 Aug 1987, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Tsang, Cecilia

LREP Sterne, Kessler, Goldstein & Fox P.L.L.C.

CLMN Number of Claims: 129

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 5060

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5591733 19970107 <--

DETD . . . solution (2.times.150 mL), with water (2.times.100 mL), and finally with brine, and dried over magnesium sulfate and evaporated to an **oil** which crystallized on standing. Flash chromatography on a silica gel bed (200 g) and eluting with hexane/ethyl acetate (90:10) recovered. . .

DETD . . . combined organic phase was extracted with more 5% hydrochloric acid and water, dried over magnesium sulfate and evaporated to an **oil** which on standing crystallized and gave 3.alpha.-toluene-p-sulphonyloxy-5.alpha.-pregnan-20-one as a white solid.

DETD . . . were washed with 700 mL of water and dried over anhydrous magnesium sulfate. The solvent was removed to give an **oil** which was crystallized from ethanol to give the titled compound (9.3 g, 416.8 g/mol, 90% yield).

DETD . . . mixture was cooled, filtered, and washed with sodium bisulfite, water, and brine, and then concentrated to give a crude reddish **oil**.

DETD The reddish **oil** above was dissolved in 150 mL of benzene and 2 mL of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU, 152 g/m, 1.02 g/mL, 13.4 mmol). . .

DETD . . . mg) was added to a solution of 3.alpha.-hydroxy-5.alpha.-pregnan-20-one (200 mg) in dry pyridine (4 mL). The stirred solution was refluxed (**oil** bath temperature set at 140.degree. C. for 4 h). The reaction mixture was cooled and poured into water and acidified. . . several times with chloroform. The organic phase was washed with water, dried over magnesium sulfate and finally concentrated to an **oil**. The crude **oil** was recrystallized from hexane and ethyl acetate to give 3.alpha.-hydroxy-5.alpha.-pregnan-20-one 3-hemisuccinate (220 mg, 84% yield) as fine white crystals.

DETD . . . methanol; the mixture was stirred at room temperature for a while. The solvent was removed in vacuo to give an **oil** which did not dissolve in ether. Addition of CH.sub.2 Cl.sub.2 gave a solution which was washed with water, 1N HCl,. . .

DETD . . . acid, microcrystalline cellulose, polymer hydrogels and the like. Typical liquid carriers are propylene glycol, aqueous solutions of .beta.-cyclodextrins, syrup, peanut **oil**, and olive **oil** and the like emulsions. Similarly, the carrier or diluent may include any time-delay material well known to the art, such. . .

DETD . . . of pharmaceutical forms can be employed. Thus, when using a solid carrier, the preparation can be plain milled micronized, in **oil**, tableted, placed in a hard gelatin or enteric-coated capsule in micronized powder or pellet form, or in the form of. . .

DETD . . . to the rodents and inhibit exploratory behavior (Christmas and Maxwell, 1970; File, 1980). A variety of clinically established anxiolytics including **diazepam**, clonazepam and pentobarbital have been shown to increase the number of transitions between the light box and the dark box,. . . in testing the anxiolytic effects of 3.alpha.-OH-DHP and 5.alpha.-THDOC. In addition, CGS-8216, a BZ antagonist, has been shown to block **diazepam**'s anxiolytic effects in the light/dark transition test (Crawley et al., 1984). To further demonstrate, in vitro, the uniqueness of the. . .

DETD . . . number of transitions between the large and small boxes was counted for 10 min. Drug pretreatment times were as follows: **diazepam** (30 min.); 3.alpha.-OH-DHP (10 min.); and 5.alpha.-THDOC (10 min.). During the antagonist studies, CGS-8216 was administered 30 min. prior to. . .

DETD The steroids 3.alpha.-OH-DHP, 3.beta.-OH-DHP, and 5.alpha.-THDOC were synthesized as described above. 2-Hydroxypropyl .beta.-cyclodextrin (.beta.-cyclodextrin) is available from Aldrich (Milwaukee, Wis.). **Diazepam** and chlordiazepoxide are available from Sigma, Co. (St. Louis, Mo.). CGS-8216 was obtained from Ciba-Geigy (Summit, N.J.). All drugs were. . .

DETD Dose-response curves for 3.alpha.-OH-DHP, 5.alpha.-THDOC and **diazepam** generated in the light/dark transition test were run over several days. The vehicle control data were analyzed across test days. . .

DETD **Diazepam**'s effects on light/dark transitions were determined. **Diazepam** produced a significant ($F(5,72)=31.6$; $p=0.0001$) inverted U-shaped dose-response curve. **Diazepam** was significantly ($p<0.01$) different from controls at 1.0, 5.0, 10, and 20 mg/kg. **Diazepam**'s maximal response was at 10 mg/kg with 86.4.+-.5.4 transitions. Though significant at 20 mg/kg, **diazepam**'s effects were diminished as compared with the effects at 10 mg/kg. These results are similar to the inverted U-shaped curves. . .

DETD . . . significant ($p<0.01$) increases alone and in the presence of CGS-8216. However, CGS-8216 was able to block the anxiolytic effect of **diazepam. Diazepam** (1.0 mg/kg) alone produced a significant ($p<0.01$) increase in transitions as compared to control. CGS-8216 did not demonstrate any intrinsic. . .

DETD . . . ($F(4,44)=18.05$; $p=0.0001$). Specifically, the steroids 3.alpha.-OH-DHP and 5.alpha.-THDOC produced significant ($p<0.01$) increases in activity as compared with control. In addition, **diazepam** produced a significant ($p<0.01$) increase in activity as compared with .beta.-cyclodextrin vehicle control. However, 3.beta.-OH-DHP did not show any effect. . .

DETD . . . Activity

DRUG	DOSE (mg/kg)	TOTAL DISTANCE (cm)
.beta.-Cyclodextrin		2004.6 .+-. 134.6
3.beta.-OHDHP	20	1979.8 .+-. 174.5

3.alpha.-OHDHP
20 5344.9 .+-. 754.5**
5.alpha.-THDOC
20 7328.4 .+-. 769.5**
DIAZEPAM 10 4817.7 .+-. 528.4**

Mice were pretreated 10 min or 30 min (**diazepam**) prior to being placed in
the center of the openfield apparatus. Total distance travelled was measured for 10 min (see. . .
DETD . . . test chambers. 3.alpha.-OH-DHP (20 mg/kg) treated mice traveled
a total distance of 5694.7.+-.608.4 cm compared with controls 2061.2 .+-.157.7 cm. **Diazepam** (10 mg/kg) had no effect on locomotor activity (2258.0.+-.897.7 cm).
CLM What is claimed is:
129. The method of claim 102 wherein the seizures are petit mal **epileptic seizures**.

L16 ANSWER 10 OF 31 USPATFULL
AB A water-dispersible tablet comprises lamotrigine, a pharmaceutically acceptable swellable clay and an additional disintegrating agent. The swellable clay and an additional disintegrating agent. The swellable clay is a smectite, e.g. Veegum F or bentonite, and is present within the granules of the tablet to provide a tablet which is capable of dispersing in water within 3 minutes to provide a dispersion which will pass through a 710 .mu.m sieve. The tablet can be optionally film-coated
in which case the dispersion time is less than 5 minutes.
AN 96:84922 USPATFULL
TI Water-dispersible tablets
IN Fielden, Krystyna E., Dartford, United Kingdom
PA Glaxo Wellcome Inc., Research Triangle Park, NC, United States (U.S. corporation)
PI US 5556639 19960917 <--
WO 9213527 19920820 <--
AI US 1993-90111 19930713 (8)
WO 1992-GB163 19920129
19930713 PCT 371 date
19930713 PCT 102(e) date
PRAI GB 1991-2019 19910131
GB 1991-24803 19911122
GB 1991-24807 19911122
GB 1991-25005 19911125
DT Utility
FS Granted
EXNAM Primary Examiner: Venkat, Jyothsna
LREP Brown, Donald, Neuner, George W.
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1664
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5556639 19960917 <--
WO 9213527 19920820 <--
SUMM . . . which can be treated by them (incorporated by reference): acyclovir (UK No.1523865), lamotrigine (EP Nos. 021 121 and 247 829), **diazepam**, paracetamol, (both commercially available), 1-(.beta.-D-arabinofuranosyl)-5-propy-1-ynyl-uracil (EP No. 0272 065),

2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone (EP No. 0123 238), allopurinol (G. B. No. 1445 983).

SUMM **Diazepam**--4 to 304 w/w, preferably 8 to 164 w/w

SUMM . . . to 5% w/w, preferably 1 to 3% w/w, zinc stearate 0.01 to 2% w/w, 0.5 to 1.5% w/w, hydrogenated vegetable **oil** 0.5 to 5% w/w, preferably 1 to 3% w/w. More suitably the lower value is 0.25%.

SUMM . . . in human medicine in the treatment of disorders of the central nervous system and in particular in the treatment of **epileptic seizures**. They may be administered one or more times per day, for example up to five times per day, at the. . . disorder being treated, the unit dose adopted and the total dose required. A suitable daily dose for the treatment of **epileptic seizures** will generally lie in the range of 5 to 500 mg., more often in the range of 25 to 400. . .

DETD . . . for each Example is as follows:

Example 41 1(D-arabinofuranosyl)-5-propynyluracil

Example 42 Allopurinol

Example 43 2[4(4-chlorophenyl)cyclohexyl3-hydroxy-1,4,napthoquinone

Example 44 Paracetamol

Example 45 **Diazepam**

IT 90-82-4 93-14-1, Guaiphenesin 103-90-2, Paracetamol 125-28-0, Dihydrocodeine 125-71-3 290-38-0D, 1,2,4-Triazine, derivs. 315-30-0, Allopurinol **439-14-5**, Diazepam 486-12-4, Triprolidine 723-46-6 738-70-5 1318-93-0, Montmorillonite, uses 2465-59-0 12174-11-7, Attapulgite 12679-43-5D, Naphthalenedione, derivs. 30516-87-1 39809-25-1 59277-89-3, Acyclovir 77181-69-2 84057-84-1, Lamotrigine 84558-93-0 87848-99-5, Acrivastine 94015-53-9 104227-87-4 119644-22-3 124832-26-4 130450-97-4 130721-33-4
(water-dispersible tablets contg.)

L16 ANSWER 11 OF 31 USPATFULL

AB The subject compounds, which are adapted for the site-specific/sustained delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D-DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain-barrier-penetrating lipoidal form of a dihydropyridine .revreaction. pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is lower alkyl or benzyl and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH functional group to the carbonyl function of [DHC], then [D] must be other than a sympathetic-stimulant, steroid sex hormone or long chain alkanol; and

(b) non-toxic pharmaceutically acceptable salts of compounds of formula (I). The corresponding ionic pyridinium salt type drug/carrier entities [D-QC].sup.+ X.sup.- are also disclosed.

AN 96:51023 USPATFULL

TI Brain-specific drug delivery

IN Bodor, Nicholas S., Gainesville, FL, United States

PA University of Florida, Gainesville, FL, United States (U.S. corporation)

PI US 5525727 19960611 <--
AI US 1992-967979 19921028 (7)
RLI Division of Ser. No. US 1991-639283, filed on 10 Jan 1991, now patented,
Pat. No. US 5187158 which is a division of Ser. No. US 1989-295938, filed on 11 Jan 1989, now patented, Pat. No. US 5008257 which is a division of Ser. No. US 1984-665940, filed on 29 Oct 1984, now patented,
Pat. No. US 4824850 which is a continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 Ser. No. Ser. No. US 1983-461543, filed on 27 Jan 1983, now abandoned Ser. No. Ser. No. US 1983-475493, filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And Ser. No. US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564
PRAI WO 1983-US725 19830519
DT Utility
FS Granted
EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Mach, D. Margaret M.
LREP Burns, Doane, Swecker & Mathis
CLMN Number of Claims: 29
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 6632
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5525727 19960611 <--
SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such
a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules
such as water and urea may pass through the. . . carrier-mediated and
active transport processes govern the movement of many molecules through
the BBB. Thus, it As generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary
combination with membrane constituents affect delivery through the. . . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .
SUMM . . . in regulating drug concentrations in the CNS. There are several
efflux processes: bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.

DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.

DETD . . . dopamine precursor used, for example, in the treatment of Parkinsonism); muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam and phenothiazine tranquilizers such as carphenazine, fluphenazine and the like; mild and strong analgesics and narcotics; sedatives and. . .

DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)-adenine; 6-azauridine; idoxuridine; trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers, such as **diazepam**, oxazepam, lorazepam, chlordiazepoxide, flurazepam, bromazepam, cnlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers/anticonvulsants such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . system for dopamine, compound 5, on administration (e.g., by injection) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enters the CNS. Following oxidation both in the brain and in the other. . . quaternary percursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic** derivatization of the catechol system in dopamine has also now been demonstrated.

DETD Accordingly, provided hereby is a potent, brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protective group(s)], which penetrates. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g., the enkephalins, which have been found to initiate **epileptic seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular injection of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionite (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . iodide, 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield,0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very slowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of

N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

. .

DETD . . . hr, after which time the precipitate was removed by filtration.

Solvents were removed at reduced pressure to give an orange **oil** which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta. [(CD.sub.3).sub.2 CO] 9.7. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta. (CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4 .multidot.1/2H.sub.2 O: C, 63.16; H,. . .

DETD . . . the solution was warmed to room temperature. After 24 hours, the solvent was removed under reduced pressure. The resulting dark **oil** was triturated with petroleum ether but no solidification occurred. Identity of the product was confirmed by NMR analysis. The product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil** . Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to give an orange **oil** . UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 : C, 64.52; H, 6.45; N,. . .

DETD . . . ether was added and then removed (10.times.5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4. Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1485## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow **oil** which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl aerate left a yellow

oil which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;. . .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1487##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to a gentle reflux and refluxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow **oil** reduced methanolic silver nitrate immediately. The structure of the product was confirmed by NMR analysis to be: ##STR1489##

DETD . . . and the solution was stirred for 4 hours. The organic layer was dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1490##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidine-dione (2 g, 0.0071 tool) was dissolved in bromoacetyl-chloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. C. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yellow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . concentration of the intermediate charged species (quaternary form) in the brain even after one single bolus injection of the starting **lipophilic** chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L16 ANSWER 12 OF 31 USPATFULL

AB This invention provides a rectally administered composition for inhibiting **epileptic seizure** and to its methods of use. The composition contains, in a suitable solvent, an anti-epileptic agent for inhibiting **epileptic seizure**, a buffer for maintaining pH, and a thickener for imparting a viscosity to the composition effective for rectal administration by injection to a

patient in **epileptic seizure**.
AN 95:96826 USPATFULL
TI Rectally-administered, **epileptic-seizure**-inhibiting composition
IN Evenstad, Kenneth L., Wayzata, MN, United States
O'Neill, Victoria A., Wayzata, MN, United States
Gorham, Thomas R., Brooklyn Park, MN, United States
PA Athena Neurosciences, Inc., San Francisco, CA, United States (U.S. corporation)
PI US 5462740 19951031 <--
AI US 1993-122685 19930917 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Azpuru, Carlos A.
LREP Merchant, Gould, Smith, Edell, Welter & Schmidt
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 691
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Rectally-administered, **epileptic-seizure**-inhibiting composition
PI US 5462740 19951031 <--
AB This invention provides a rectally administered composition for inhibiting **epileptic seizure** and to its methods of use. The composition contains, in a suitable solvent, an anti-epileptic agent for inhibiting **epileptic seizure**, a buffer for maintaining pH, and a thickener for imparting a viscosity to the composition effective for rectal administration by injection to a patient in **epileptic seizure**.
SUMM This invention relates to rectally administered compositions for inhibiting **epileptic seizure** and to their methods of preparation and application.
SUMM . . . dysrhythmia characterized by an abnormal and excessive EEG (electroencephalograph) discharge and by a disturbance of consciousness.
During an episode of **epileptic seizure**, there may be involuntary body movement or hyperactivity of the autonomic nervous system. Different kinds of **epileptic seizures** can display various clinical phenomena and EEG activities. Such variations in clinical phenomena and EEG activities form the basis of. . .
SUMM Generally, it is desirable to prevent **epileptic seizures** in humans by maintaining effective drug therapy. However, if seizure takes place, particularly for seizures with extensive tonic-clonic duration, such. . . the patient, such as bruises, cuts, broken arms or even damage caused by anoxia. Anti-epileptic drugs (i.e., drugs that inhibit **epileptic seizure**, either before or after the onset of **epileptic seizure**) can be given intravenously for acute inhibition of the **epileptic seizure**. See "Drugs for Epilepsy", The Medical Letter, Vol. 31, Issue 783, 1-4, 1989. However, in situations in
which there is. . . drugs is not desirable because the patient's uncontrolled movement may hinder injection or even cause injuries. Moreover, intravenous injection of **diazepam**, a preferred anti-epileptic drug, is sometimes painful and can cause thrombophlebitis, an inflammation of a vein associated with thrombus formation.. . .
SUMM . . . as anti-epileptic agents. See Remington's Pharmaceutical Sciences, supra. A convenient way to administer an anti-epileptic drug

such as benzodiazepine, e.g. **diazepam**, is by ingestion so that the drug can be absorbed by the gastro-intestinal tract. Sheth et al. (U.S. Pat. No. 4,126,672) describe a sustained-release capsule for oral administration of **diazepam**. The capsules contain medicaments in combination with a hydrocolloid. Upon contact with gastric fluid, the hydrocolloid hydrates, forming an outside. . .

SUMM . . . anti-convulsive agent into a shapable base material. Suitable suppository bases are described to include cocoa butter, glycerinated gelatin, hydrogenated vegetable **oils**, mixtures of polyethylene glucose, and fatty acid esters of polyethylene glycol.

SUMM . . . suppositories are slow-acting and therefore not effective for rendering fast relief of seizure. Therefore, there is a need for an **epileptic-seizure**-inhibiting composition that can be administered and absorbed quickly and safely.

SUMM The present invention provides a viscous, aqueous-based, **epileptic-seizure**-inhibiting composition effective to inhibit **epileptic seizure**. The composition is suitable for rectal administration by injection with a syringe-like applicator. The present invention is also directed to. . . and cartridges containing the composition and methods of using the assemblies and cartridges for delivery of the present composition. The **epileptic-seizure**-inhibiting composition is preferably a thickened solution that contains these ingredients: solvent, an anti-epileptic agent for inhibiting **epileptic seizure** , a pH adjusting agent such as a buffer system for maintaining a pH suitable for rectal administration, and a thickener. . . for imparting a viscosity to the composition effective for rectal administration by injection to a patient in or threatened by **epileptic seizure**.

DETD One embodiment of the present invention is a composition for inhibiting **epileptic seizures** in a patient, such as status epilepticus seizures, acute cluster epilepsy seizures, acute repitctue seizures and febrile seizures. The composition. . . retained inside the patient's rectum without substantial leakage or drainage therefrom. The composition is useful for inhibiting or moderating an **epileptic seizure** in a patient during seizure. However, it can also be used to prevent the onset of seizure.

DETD A wide variety of anti-epileptic agents are known in the art. Many may be utilized in the **epileptic-seizure**-inhibiting composition of this invention. Representative examples of effective anti-epileptic agents include ethynyl amines such as deprenyl, eldeprine and eidepryl barbiturates such as mephobarbital, febarbamate, primidone, and phenobarbital sodium, benzodiazepines such as carbamezepine, lorazepam, and **diazepam**, hydantoins such as phenytoin sodium, mephenytoin and ethotoin BP, oxazolidinediones such as paramethadione and trimethadione, succinimides such as phensuximide and. . .

DETD When a patient is in **epileptic seizure**, in order to minimize injury to the patient due to tonic spasm and clonic movement, prompt administration of medication is. . . many anti-epileptic agents, such as phenobarbital, can be used in the invention, the drug of choice is a benzodiazepine, particularly **diazepam**. Because of their relaxing effect in skeletal muscles, benzodiazepines, particularly **diazepam**, are also useful in the present invention for treating various types of epilepsies involving skeletal muscle contraction or spasm.

DETD . . . more anti-epileptic agents in the composition of the present invention. When two or more anti-epileptic agents are present in an **epileptic-seizure**-inhibiting composition, it is important to ensure that there is no deleterious interaction between the anti-epileptic agents so as not to. . .

DETD . . . 0.1-2.5 wt-% of the total composition, preferably about 0.25-1.5 wt-% to about 7.5 wt-%. In the preferred embodiment in which **diazepam** is the only anti-epileptic agent in the composition, the concentration of **diazepam** is typically about 0.25-0.75 wt-% of the composition.

DETD Preferably, a dose of **epileptic-seizure**-inhibiting composition is selected so that the effective amount of the anti-epileptic agent is in a suitable volume for a particular. . . a composition of the present invention contains an amount of an anti-epileptic agent which is therapeutically effective to inhibit an **epileptic seizure**. This amount will depend on the particular anti-epileptic agent used. For commercially available anti-epileptic agents, information on the therapeutically effective amount for inhibiting **epileptic seizure** is available to the public.

DETD Typically, the present composition can be administered so that single doses of **diazepam** of about 7.5 mg to 20 mg are delivered to an adult, so as to achieve a dose in the. . . mg/kg. The amount can vary depending on the size and physical condition of the individual. The volume of the present **epileptic-seizure**-inhibiting composition to be administered also will vary with different patients. As a general guideline for using the composition of the present invention, e.g., wherein 0.5 wt-% **diazepam** is the anti-epileptic agent, typically the dosage is about 1.5 ml to about 5 ml for an adult (>12 years),. . .

DETD The **epileptic-seizure**-inhibiting composition of the present invention contains an amount of a thickener effective for rendering the consistency of the composition effective for rectal administration to a patient in **epileptic seizure** by injection. To be effective as an injectable, rectally administered **epileptic-seizure**-inhibiting composition, the present composition preferably has a viscosity such that it can be quickly administered by injection, yet once administered,. . .

DETD . . . thickeners is used to provide a viscosity within the desired range. The amount of a particular thickener used in the **epileptic-seizure**-inhibiting composition is dependent on the particular thickener used. Typically, the concentration of a suitable thickener such as a cellulose ether. . .

DETD . . . is about 7.0. The optimal pH for stability for some anti-epileptic agents is slightly lower than 7. For example, for **diazepam** stability, the optimal pH is about 5.5. It is preferred that the pH of the present composition be adjusted to. . . is acceptable for rectal administration and stability of the anti-epileptic agent. Therefore, typically, the pH of the present composition containing **diazepam** will be neutral or mildly acidic, e.g., about 5.5 to 7.5. Preferably, the pH is about 6.2 to 7.2.

DETD . . . often an anti-epileptic agent supplied in solution form contains suitable pH adjusting agents. One can vary the pH of the **epileptic-seizure**-inhibiting composition by fine-tuning the amount of the pH adjusting agents. For the preferred embodiment with **diazepam** as the anti-epileptic agent, the

concentration of benzoic acid can be about 0.01 to 10 wt-% of the composition and. . .

DETD . . . the precipitation thereof. Depending on the particular anti-epileptic agent, different organic solvents may be used. In the preferred case, wherein **diazepam** is the anti-epileptic agent, 1-2 nontoxic polyols or alkanols such as, propylene glycol and/or ethyl alcohol may be used as. . .

DETD . . . rectum, an organic solvent that can act as a physiologically-acceptable liquid surfactant can be selected to be included in the **epileptic-seizure**-inhibiting composition. An effective surfactant can modify the surface tension of the composition of the invention and facilitate coating of the. . .

DETD . . . solvent or solvents are used in amounts effective to solubilize the anti-epileptic agent and to inhibit precipitation thereof in the **epileptic-seizure**-inhibiting composition, e.g., about 25 to 75 wt-% of a polyol or polyol-alkanol mixture may be employed. In the preferred embodiment in which the **epileptic-seizure**-inhibiting composition contains **diazepam** as the anti-epileptic agent, typically, propylene glycol is present at a concentration of about 25 wt-% to about 60 wt-%. . .

DETD A physiologically-acceptable preservative can be optionally included in the **epileptic-seizure**-inhibiting composition to extend the shelf-life of the composition against bacterial attack. Benzyl alcohol is the preferred preservative, although other preservatives,. . . concentration of the preservative needed in a composition varies with the preservative selected. Typically, a preservative is present in the **epileptic-seizure** -inhibiting composition at a concentration of about 0.01 wt-% to about 2.5 wt-% of the composition. For benzyl alcohol, the preferred. . .

DETD F. Preparation of the **Epileptic-seizure**-inhibiting Composition

DETD G. Administration of the **Epileptic-seizure** -inhibiting Composition

DETD The **epileptic-seizure**-inhibiting composition is preferably applied to the rectum by an applicator. Typically, the applicator is similar to a syringe. A preferred. . . seizure. The applicator further has a pressuring means associated with or operatively connected to the syringe barrel for forcing the **epileptic-seizure**-inhibiting composition out of the syringe barrel, through the elongated hollow member and into the rectum. For example, the pressuring means. . .

DETD . . . the applicator is made of a material that does not absorb or chemically react with the anti-epileptic agents in the **epileptic -seizure**-inhibiting composition. This is particularly important if the composition is stored in the applicator for an extended period of time. For. . . constructed of a plastic material and another part with glass or metal. For example, a glass cartridge filled with a **diazepam**-containing composition can be inserted into an applicator having a plastic barrel. Because the glass cartridge is surrounded by the plastic. . .

DETD . . . tip member of the applicator in the rectum of the patient, and apply pressure to the barrel to deliver the **epileptic-seizure**-inhibiting composition into the rectum of the patient. It is also preferred to package a specific, premeasured amount of the composition. . .

DETD . . . first end 41 of a cylindrical barrel 40. A generally cylindrical cartridge 50 containing internally a premeasured volume of

an **epileptic-seizure**-inhibiting composition (not shown) and a plunger 60 effective for forcing the composition out of the cartridge 50 can be inserted. . .

DETD The cartridge 50 that can contain the **epileptic-seizure**-inhibiting composition has a hollow cylindrical body portion 55 connected on one end to a hollow neck portion 57 and connected. . .

DETD The applicator 10, including the body 20, the cartridge 50 containing the **epileptic-seizure**-inhibiting composition, and the plunger 60, can be packaged as a unit. The neck portion 57 of the cartridge has an. . . 40. The elongated, hollow member 30 of the applicator 10 is then inserted into the rectum of the patient. The **epileptic-seizure**-inhibiting composition is then administered to the patient by the operator manually engaging the finger grips 70 and the flange 66. . .

DETD Other embodiments of applicator may have flexible bulb-shaped bodies in which the **epileptic-seizure**-inhibiting composition of the present invention is stored. In use, the composition can be forced out of the bulb-shaped body into. . .

DETD While orally and intravenously administered **epileptic-seizure**-inhibiting compositions are not conveniently given to a patient in seizure with tonic spasm and clonic movement, the composition of the present invention is advantageously so employed. The composition of this invention is effective to inhibit **epileptic seizure** because it can be administered into the rectum in seconds and the anti-epileptic agent in the composition is absorbed quickly. . .

DETD The **epileptic-seizure**-inhibiting composition has a viscosity that is low enough that it can be inserted in seconds by using, for example, a. . . absorbed may be unreasonably long for the purpose of inhibiting seizure that is in progress. Clinical studies has shown that **diazepam** suppositories are inappropriate where a rapid effect is required (see Hughes et al., Aust J. Hosp. Pharm., 14:2, 73-75 (1984)).. . .

DETD In intravenously administration of **epileptic-seizure**-inhibiting compositions, the pH of the **epileptic-seizure**-inhibiting composition is maintained at a range that is compatible with the intravenous route of administration. The pH for an intravenously. . . be suitable because there is a less risk of adversely affecting the pH of the blood. As a result, the **epileptic-seizure**-inhibiting composition can have a longer shelf life than intravenous solutions.

DETD **Epileptic-seizure**-inhibiting Composition

DETD . . . benzoic acid USP (0.305 kg) was added into the mixture through a 20 mesh screen and mixed for ten minutes. **Diazepam**, USP (0.128 kg), was added into the mixture and mixed for an additional 20 minutes. Hydroxypropylmethyl cellulose, METHOCEL.TM. E50 LVP. . .

DETD **Epileptic-seizure**-inhibiting Composition

DETD An **epileptic-seizure**-inhibiting composition is made using a procedure analogous to that of Example 1 except 1.0 kg of phenobarbital sodium, USP (Windthrop) is used instead of 0.128 kg of **diazepam**.

DETD **Epileptic-seizure**-inhibiting Composition

DETD An **epileptic-seizure**-inhibiting composition is made using a procedure analogous to that of Example 1 except 0.128 kg of phenytoin sodium, USP (Park-Davis) is used instead of 0.128 kg of

diazepam.

DETD A comparative, randomized single-dose 2-way crossover bioavailability with the **diazepam** viscous solution of Example 1 and Roche **diazepam** (valium.RTM.) injectable solution was conducted using as subjects 18 healthy adult males, age 18-45 years. A dosage of 15 mg. . .

DETD . . . present rectal solution was 90.4% relative to the Roche injectable solution. Half-lives were similar and the maximum serum concentrations of **diazepam** (447 ng/ml for the present composition and 584 ng/ml for the Roche injectable) were both above the effective therapeutic concentration. . .

DETD Use of the **Epileptic-seizure**-inhibiting Composition

DETD When a adult patient is observed to have an **epileptic seizure** attack, the kit of Example 1 is opened and the applicator assembled by opening the sealed end of the cartridge. . .

CLM What is claimed is:

1. A viscous, **epileptic-seizure**-inhibiting composition comprising: (a) about 0.1-2.5 wt-% of the total composition of an anti-epileptic agent; (b) a buffer system in an. . .

3. The composition of claim 2 wherein the anti-epileptic agent is **diazepam**.

8. A viscous, **epileptic-seizure**-inhibiting composition comprising: (a) about 0.25-0.75 wt-% **diazepam**; (b) a buffer system in an amount effective to maintain the pH of the composition at about 5.5-7.5; (c) about. . .

IT **439-14-5**, Diazepam
(rectal antiepileptic compns.)

L16 ANSWER 13 OF 31 USPATFULL

AB A method for administering a therapeutically effective amount of a biologically active substance to the circulatory system of a mammal including administering a pharmaceutical composition having a total volume of 1-1000 .mu.l to a nasal mucosal membrane of the mammal, the pharmaceutical composition including the therapeutically effective amount of the biologically active substance dissolved or suspended in a volume of 1-1000 .mu.l of a n-glycofurol-containing vehicle including at least one n-glycofurol represented by the formula: ##STR1## wherein n is from 1 to 8, so that upon administration of the pharmaceutical composition to the nasal mucosal membrane, absorption of the biologically active substance through the mucosal membrane and into the blood stream of the mammal rapidly takes place and thereby allows the biologically active substance to exert its therapeutic effect.

AN 95:58110 USPATFULL

TI Method of administering a biologically active substance

IN Bechgaard, Erik, Hellerup, Denmark
Gizurarson, Sveinbjorn, Keflavik, Iceland
Hjortkjaer, Rolf K., Humlebaer, Denmark

PA Bechgaard International Research and Development A/S, Hellerup, Denmark (non-U.S. corporation)

PI US 5428006 19950627 <--

AI US 1993-151802 19931115 (8)

DCD 20120314

RLI Continuation of Ser. No. US 1993-71604, filed on 4 Jun 1993, now abandoned which is a continuation of Ser. No. US 1992-870893, filed on 20 Apr 1992, now abandoned which is a division of Ser. No. US 1991-696564, filed on 8 May 1991, now abandoned

DT Utility
FS Granted
EXNAM Primary Examiner: Warden, Jill; Assistant Examiner: Davenport, A. M.
LREP Evenson, McKeown, Edwards & Lenahan
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 12 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 1468
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5428006 19950627 <--

SUMM . . . be biocompatible with the mucus and hence have a certain degree of hydrophilicity. However, the vehicle should preferably also posses **lipophilic** properties in order to dissolve a physiologically active amount of certain biologically active substances.

SUMM Lau and Slattery (1989) studied the absorption characteristics of **diazepam** and lorazepam following intranasal administration for the treatment of status epilepticus. In order to solubilize these drugs, a non-ionic surfactant, polyoxyethylated castor **oil**, was selected as the least irritating out of several solvents studied including polyethyleneglycol 400. **Diazepam** absorption was 84 and 72%, respectively, in two adults measured over a period of 60 hours. However, the peak concentration. . . peak (2.3 hours). The authors conclude that the intranasal route of administration had limited potential for the acute treatment of **epileptic seizures**.

SUMM International Patent Publication No. WO 86/04233 discloses a pharmaceutical composition wherein the drug (e.g. **diazepam**) is dissolved in a mixture of propellant and co-solvent e.g. glycerolphosphatide. This composition requires a pressurized system and at least. . .

SUMM . . . anti-emetica having a regulatory effect on the motility of the intestine such as domperidom; Anti-epileptica and anti-spasmolytica such as clonazepam, **diazepam**, nitrazepam, lorazepam etc.; Anti-histaminic and histaminic agents such as diphenhydramin HCl, chloropheniramine maleate, clemastine, histamine, prophenpyridamine maleate, chlorprophenpyridamine maleate, disodium. . . citrate or .alpha..sub.1 -antitrypsin etc.; Sedatives such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, lorazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. . . and synthetic modifications thereof etc.; Tranquillisers such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. . .

SUMM . . . derivatives and analogues thereof; and tranquilizer such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam,

haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,.

.

SUMM . . . invention, the active substance is selected among antiepileptica, spasmolytics and tranquillisers selected from the group of benzodiazepines such as clonazepam, **diazepam**, flunitrazepam, triazolam, lorazepam, nitrazepam or mixtures thereof.

SUMM . . . preparation additionally comprises one or more compound(s) selected from the group consisting of surfactants, absorption promoters, water absorbing polymers, microspheres, **oils**, emulsions, liposomes, substances that inhibit enzymatic degradation, alcohols, organic solvents, water, hydrophobic agents, pH-controlling agents, preservatives and osmotic pressure controlling. . .

SUMM . . . [9004 76-6]). Glycofurol 75 is a colourless liquid miscible with water, alcohols, such as methanol, ethanol, n-propanol, glycerol and various **oils** in all proportions and has a b.p. about 155.degree. C. GF is reported to cause irritation when used in compositions. . .

SUMM A special advantage in using the above vehicle system is that e.g. highly **lipophilic** substances such as the benzodiazepines as well as water soluble substances e.g. peptides and proteins such as the pancreatic hormones. . . relevant dose for human subjects in only e.g. 25-300 .mu.l of the vehicle. In aqueous solutions clinically relevant doses of **diazepam** and clonazepam will alternatively have to be dissolved in about 5000 ml and >10 ml, respectively.

SUMM The vehicle system according to the invention may be used in combination with various co-solvents, such as vegetable **oil** such as Miglyol.RTM. 840 (Dynamit Nobel Chemie, Troisdorf, W-Germany) or optionally hydrogenated or ethoxylated castor **oil**, which surprisingly increases the possibilities for designing a controlled release-formulation such as a **diazepam** formulation which avoids peak plasma concentrations.

SUMM . . . according to the invention may comprise one or more additional pharmaceutical exipients, such as: surfactants and absorption promoters having a hydrophillic-**lipophilic** balance from about 6 to 26 and ionic as well as non-ionic surfactants including polyoxyethylene alcohol ethers, bile salts and. . . aprotinin; Alcohols, such as, ethanol, glycerol, or benzylalcohol; Organic solvents, such as, ethylacetate, or benzylalcohol; Hydrophobic agents, such as vegetabile **oil**, e.g. soybean **oil**, peanut **oil**, coconut **oil**, corn **oil**, olive **oil**, sunflower **oil**, castor **oil**, Miglyol.RTM. 810/812/840 or mixtures thereof; pH-controlling agents, such as, nitric acid, phosphoric acid, or acetic acid, citrate; Preservatives and osmotic. . .

DRWD FIG. 6 shows a graphical representation showing the mean plasma level of **diazepam** after administration of preparations comprising glycofurol and various co-solvents,

DETD . . . 4 30 .mu.l F in PEG

1

20

21

22 f

23

24

25 m 5 30 .mu.l F in PEG + GF

1

26
27
28 f
29
30

Abbreviations:
D = **Diazepam** 3%; L = Lorazepam 5%;
F = Flunitrazepam 1%; PEG = Polyethylene glycol 200;
GF = Glycofurol 75; PEG + GF =. . .

DETD 3 mg **diazepam** in 100 .mu.l vehicle was prepared and applied to rabbits in a manner analogous to that described in example 6. The following vehicles were used: (1) Glycofurolum 75 (GF); (2) Miglyol 840+GF (7+3) and (3) Vegetable **oil**+GF (7+3). Blood samples were obtained from the marginal ear vein at following time intervals: 0,

5, 10, 15, 30 and 60 minutes and the **diazepam** concentration was determined by HPLC.

DETD FIG. 6 shows the mean plasma **diazepam** concentrations obtained after the intranasal administration. An initial peak plasma concentration can be controlled dependent on the GF/**oil** vehicle used. The plasma concentration for the GF formulation at 5 minutes is about 55% of an intravenous injection of 3 mg **diazepam** as Stesolid.RTM. (Dumex A/S, Denmark).

DETD Surprisingly it has been found that the intranasal absorption of e.g. benzodiazepines, such as clonazepam and **diazepam**, in the vehicles according to the invention is very similar to an intravenous injection (i.v.). From FIG. 1 it appears. . .

DETD . . . dose volume is desirable in order to reduce or eliminate local irritating effect. Alternatively a non irritating co-solvent, e.g. vegetabile **oil**, may be added. In this way a desired dose volume or delivery rate may also be obtained. To reduce plasma. . .

DETD Lau, S. W. J. and Slattery, J. T. (1989), "Absorption of **diazepam** and lorazepam following intranasal administration." International Journal of Pharmaceutics, 54,171-174.

CLM What is claimed is:

. . . method according to claim 5 wherein the benzodiazepine is at least one member selected from the group consisting of clonazepam, **diazepam**, flunitrazepam, triazolam, lorazepam, and nitrazepam.

10. A method according to claim 5 wherein the benzodiazepine is **diazepam**.

~~14. A method according to claim 1 wherein the vehicle further comprises~~ a vegetable **oil**.

IT 50-56-6, Oxytocin, biological studies 50-57-7, Lypressin 146-22-5, Nitrazepam **439-14-5**, Diazepam 846-49-1, Lorazepam 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 9001-25-6, Blood coagulation factor VII 9001-27-8, Blood coagulation factor VIII 9001-28-9, Blood coagulation factor IX 9002-67-9, LH 9002-68-0, FSH 9002-72-6, Growth hormone 9004-10-8, Insulin, biological studies 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9034-40-6, LHRH 11000-17-2, Vasopressin 16679-58-6, DDAVP 28911-01-5, Triazolam 50647-00-2, LTH 58822-25-6, Leucine enkephalin 63631-40-3, DADLE 66960-34-7, Metkephamid
(pharmaceutical intranasal formulation contg.)

L16 ANSWER 14 OF 31 USPATFULL

AB A pharmaceutical preparation for application of an effective amount of

one or more biologically active substance(s) to a mucosal membrane of a mammal comprising an n-glycofurol represented by the formula I:

##STR1##

wherein n is 1 to 4 in an amount from: 0.1-30% preferably 0.1-20% most preferably 1-15% in water, or in vegetable **oil** or n-ethylene glycol(s) represented by formula II:

H(OCH.sub.2 CH.sub.2).sub.p OH

wherein p is 2 to 8, or in a mixture thereof. Nasal administration of the preparation produces a high plasma concentration of the pharmaceutically active substance(s) nearly as rapid as by i.v. administration.

AN 95:22893 USPATFULL
TI Pharmaceutical preparation
IN Bechgaard, Erik, Hellerup, Denmark
Gizurarson, Sveinbjorn, Keflavik, Iceland
Hjortkjaer, Rolf K., Humlebaer, Denmark
PA Bechgaard International Research and Development A/S, Hellerup, Denmark (non-U.S. corporation)
PI US 5397771 19950314 <--
AI US 1993-118683 19930910 (8)
RLI Continuation of Ser. No. US 1991-791651, filed on 14 Nov 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-696564, filed on 8 May 1991, now abandoned
PRAI DK 1990-1170 19900510
DK 1990-2075 19900830
DT Utility
FS Granted
EXNAM Primary Examiner: Lee, Lester L.; Assistant Examiner: Davenport, A. M.
LREP Wegner, Cantor, Mueller & Player
CLMN Number of Claims: 29
ECL Exemplary Claim: 1
DRWN 16 Drawing Figure(s); 16 Drawing Page(s)
LN.CNT 1854
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5397771 19950314 <--
AB . . . n is 1 to 4 in an amount from: 0.1-30% preferably 0.1-20% most preferably 1-15% in water, or in vegetable **oil** or n-ethylene glycol(s) represented by formula II:
SUMM . . . be biocompatible with the mucus and hence have a certain degree of hydrophilicity. However, the vehicle should preferably also posses **lipophilic** properties in order to dissolve a physiologically active amount of certain biologically active substances.
SUMM Lau and Slattery (1989) studied the absorption characteristics of **diazepam** and lorazepam following intranasal administration for the treatment of status epilepticus. In order to solubilize these drugs, a non-ionic surfactant. polyoxyethylated castor **oil**, was selected as the least irritating out of several solvents studied including polyethyleneglycol 400. **Diazepam** absorption was 84 and 72%, respectively, in two adults measured over a period of 60 hours. However, the peak concentration. . . peak (2.3 hours). The authors conclude that the intranasal route of administration had limited potential for the acute treatment of **epileptic seizures**.
SUMM International Patent Publication No. WO 86/04233 discloses a pharmaceutical composition wherein the drug (e.g. **diazepam**) is

dissolved in a mixture of propellant and co-solvent e.g. glycerolphosphatide. This composition requires a pressurized system and at least. . .

SUMM wherein p is an integer of 3-8 or in water or in a vegetable **oil** or in a mixture of water and/or n-ethylene glycol and/or vegetable **oil**.

SUMM . . . anti-emetica having a regulatory effect on the motility of the intestine such as domperidon; Anti-epileptica and anti-spasmolytica such as clonazepam, **diazepam**, nitrazepam, lorazepam etc.; Anti-histaminic agents and histaminic agents such as diphenhydramin HCl, chloropheniramine maleate, clemastine, histamine, prophenpyridamine maleate, chlorprophenpyridamine maleate,. . . citrate, or .alpha..sub.1 -antitrypsin etc.; Sedatives such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. . . and synthetic modifications thereof etc.; Tranquillisers such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. . .

SUMM . . . derivatives and analoguss thereof; and tranquilizer such as alpazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. . .

SUMM . . . invention, the active substance is selected among antiepileptica, spasmolytics and tranquilizers selected from the group of benzodiazepines such as clonazepam, **diazepam**, flunitrazepam, triazolamn, lorazepam, nitrazepam or mixtures thereof.

SUMM . . . in addition to the biologically active substance(s). Such carrier may comprise water and/or n-ethylene glycol and/or propylene glycol and/or vegetable **oil** and/or even powdery carrier of e.g. microspheres.

SUMM . . . minor proportions of one or more compound(s) selected from the group consisting of surfactants, absorption promoters, water absorbing polymers, microspheres, **oils**, emulsions, liposomes, substances that inhibit enzymatic degradation, alcohols, organic solvents, water, hydrophobic agents, pH-controlling agents, preservatives and osmotic pressure controlling. . .

SUMM wherein p is 3 to 8 or in water or in a vegetable **oil** or in a mixture of water and/or n-ethylene glycol and/or vegetable **oil**.

SUMM wherein p is 3 to 8 or in water or in a vegetable **oil** or in a mixture of water and/or n-ethylene glycol and/or vegetable **oil** for application to a mucosal membrane.

SUMM . . . [9004 76-6]). Glycofurol 75 is a colourless liquid miscible with water, alcohols, such as methanol, ethanol, n-propanol, glycerol

and various **oils** in all proportions and has a b.p. about 155.degree. C. GF is reported to cause irritation when used in compositions. . .

SUMM A special advantage in using the above vehicle system is that e.g. highly **lipophilic** substances such as the benzodiazepines as well as water soluble substances e.g. peptides and proteins such as the pancreatic hormones. . . relevant dose for human subjects in only e.g. 25-300 .mu.l of the vehicle. In aqueous solutions clinically relevant doses of **diazepam** and clonazepam will alternatively have to be dissolved in about 5000 ml and >10 ml, respectively.

SUMM The vehicle system according to the invention may be used in combination with various co-solvents, such as vegetable **oil** such as Miglyol.RTM. 840 (Dynamit Nobel Chemie, Troisdorf, W-Germany) or optionally hydrogenated or ethoxylated castor **oil**, which surprisingly increases the possibilities for designing a controlled release--formulation such as a **diazepam** formulation which avoids peak plasma concentrations.

SUMM . . . according to the invention may comprise one or more additional pharmaceutical exipients, such as: surfactants and absorption promoters having a hydrophillic-**lipophilic** balance from about 6 to 26 and ionic as well as non-ionic surfactants including polyoxyethylene alcohol ethers, bile salts and. . . aprotinin; Alcohols, such as, ethanol, glycerol, or benzylalcohol; Organic solvents, such as, ethylacetate, or benzylalcohol; Hydrophobic agents, such as vegetabile **oil**, e.g. soybean **oil**, peanut **oil**, coconut **oil**, corn **oil**, olive **oil**, sunflower **oil**, castor **oil**, Miglyol.RTM. 810/812/840 or mixtures thereof; pH-controlling agents, such as, nitric acid, phosphoric acid, or acetic acid, citrate; Preservatives and osmotic. . .

DRWD FIG. 6 shows a graphical representation showing the mean plasma level of **diazepam** after administration of preparations comprising glycofurol and various solvents,

DETD . . . .mu.l F in PEG 1

20
21
22 f
23
24
25 m 5 30 .mu.l F in PEG + GF 1
26
27
28 f
29
30

Abbreviations:
D = **Diazepam** 3%; L = Lorazepam 5%; F = Flunitrazepam 1%; PEG = Polyethylene glycol 200; GF = Glycofurol 75; PEG +. . .

DETD 3 mg **diazepam** in 100 .mu.l vehicle was prepared and applied to rabbits in a manner analogous to that described in example 6. The following vehicles were used: (1) Glycofurolum 75 (GF); (2) Miglyol 840+GF (7+3) and (3) Vegetable **oil**+GF (7+3). Blood samples were obtained from the marginal ear vein at following time intervals: 0, 5, 10, 15, 30 and 60 minutes and the **diazepam** concentration was determined by HPLC.

DETD FIG. 6 shows the mean plasma **diazepam** concentrations obtained after the intranasal administration. An initial peak plasma concentration can be controlled dependent on the GF/**oil** vehicle used. The plasma concentration for the GF formulation at 5 minutes is about 55% of an intravenous injection of 3 mg **diazepam** as Stesolid.RTM. (Dumex A/S, Denmark).

DETD Surprisingly it has been found that the intranasal absorption of e.g. benzodiazepines, such as clonazepam and **diazepam**, in the vehicles according to the invention is very similar to an intravenous injection (i.v.). From FIG. 1 it appears. . .

DETD . . . volume is desirable in order to reduce or eliminate a local irritating effect. Alternatively a non irritating co-solvent, e.g. vegetabile **oil**, may be added. In this way a desired dose volume or delivery rate may also be obtained. To reduce plasma. . .

DETD TABLE 2

THE INFLUENCE OF GLYCOFUROLE (% GF) IN TETRAETHYLENEGLYCOL (4EG) AND VEGETABLE **OIL** (OV)
IN GF ON THE TIME TO RESPONSE (minutes) AFTER INTRANASAL APPLICATION OF 0.25 mg CLONAZEPAM TO
RABBITS (n = 4).
NOTICE: THE TIME. . .

DETD Lau, S. W. J. and Slattery, J. T. (1989), "Absorption of **diazepam** and lorazepam following intranasal administration." International Journal of Pharmaceutics, 54, 171-174.

CLM What is claimed:

. . . n is from 1 to 4, the vehicle further comprising a component selected from the group consisting of water, vegetable **oil**, n-ethylene glycol(s) represented by the formula II: H(OCH.sub.2 CH.sub.2).sub.p OH wherein p is 3 to 8, and mixtures thereof, so. . .

. . . 13. The method according to claim 12, wherein the biologically active substance is selected from the group consisting of clonazepam, **diazepam**, flunitrazepam, triazolam, lorazepam, nitrazepam and mixtures thereof.

. . . n is from 1 o 4, the vehicle further comprising a component selected from the group consisting of water, vegetable **oil**, n-ethylene glycol(s) represented by the formula II: H(OCH.sub.2 CH.sub.2).sub.p OH wherein p is 3 or 4, and mixtures thereof.

. . . pharmaceutical composition according to claim 22, wherein the biologically active substance is selected from the , group consisting of clonazepam, **diazepam**, flunitrazepam, triazolam, iorazepam, bitrazepam and mixtures thereof.

IT 50-56-6, Oxytocin, biological studies 50-57-7, Lypressin 146-22-5, Nitrazepam **439-14-5**, Diazepam 846-49-1, Lorazepam 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 9001-25-6, Blood coagulation factor VII 9001-27-8, Blood coagulation factor VIII 9001-28-9, Blood coagulation factor IX 9002-67-9, LH 9002-68-0, FSH 9002-72-6, Growth hormone 9004-10-8, Insulin, biological studies 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9034-40-6, LHRH 11000-17-2, Vasopressin 16679-58-6, DDAVP 28911-01-5, Triazolam 50647-00-2, LTH 58822-25-6, Leucine enkephalin 63631-40-3, DADLE 66960-34-7, Metkephamid
(pharmaceutical intranasal formulation contg.)

L16 ANSWER 15 OF 31 USPATFULL

AB It has been discovered that certain (+)-3-substituted-N-alkylmorphinans areffective anticonvulsant and neuroprotective agents. Novel compounds having these biological properties are presented in a method of use for preventing, treating or controlling convulsions in mammals having a need for such treatment. The compounds do not lead to dependency, have low toxicity, and provide effective anticonvulsant or neuroprotective treatment with little or no behavioral detriment to the recipient. A number of pharmacological formulations and methods of administering compounds of the invention are suitable for anticonvulsive or neuroprotective treatments.

AN 93:91640 USPATFULL

TI (+)-3-substituted-N alkylmorphinans, synthesis and use as anticonvulsant and neuroprotective agents

IN Newman, Amy H., Silver Spring, MD, United States
Tortella, Frank C., Columbia, MD, United States

PA The United States of America as represented by the Secretary of the Army, Washington, DC, United States (U.S. government)

PI US 5258386 19931102 <--

AI US 1991-715084 19910605 (7)

DT Utility

FS Granted

EXNAM Primary Examiner: Daus, Donald G.

LREP Bellamy, Werten F. W., Moran, John F.

CLMN Number of Claims: 10

ECL Exemplary Claim: 5

DRWN 3 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 613

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5258386 19931102 <--

SUMM . . . U.S. Pat. No. 4,906,638 that dextromethorphan has a potentiating effect on certain antiepileptic or antiseizure compounds such as diphenylhydantoin, phenobarbital, **diazepam** ketamine, and carbamazepine. The pharmacological use of dextromethorphan has at least one major disadvantage, however, in that it metabolizes rapidly. . .

SUMM . . . anticonvulsant agents and combinations are known, but toxicity and other dosage-dependent symptoms remain as challenges to the pharmacological control of **epileptic seizures** and other kinds of convulsions. Another manifestation of this symptomatology is the interference by some anticonvulsants with the availability in. .

DETD . . . 151 [1968] resulted in decomposition of the ether. The ether was converted to 4 in moderate yield by using mineral **oil** as the solvent. Basic hydrolysis to an iminocarboxylic acid intermediate followed by acidic hydrolysis yielded 5 which was purified with. . .

DETD Compound 3 (10.0 g, 21.7 mmol) was placed in 100 mL mineral **oil** (light white **oil**, Sigma), under a stream of argon and was stirred vigorously and carefully heated in a sand bath to 330.degree.-340.degree. C.. . . filtered through a pad of "flash" silica gel. The mixture was eluted with 700 mL ether to remove all mineral **oil** and the receiving flask was changed and the product was eluted with 800 mL CHCl.sub.3 :CH.sub.3 OH:NH.sub.4 OH (90:10:1) to. . .

DETD . . . ether. The combined organic fraction was washed with 1.times.10

mL water, dried with sodium sulfate, and evaporated to pale yellow **oil** (0.53 g, 93%) which was nearly homogeneous by TLC. The crude free base was dissolved in hot 2-propanol and added. . .

DETD . . . with 1.times.25 mL water, dried with sodium sulfate and evaporated to 0.98 g (89%) of crude 8 as a dark **oil**. Purification by gradient flash column chromatography (CHCl.sub.3 :CH.sub.3 OH:NH.sub.4 OH 95:5:1/90:10:1) yielded 0.59 g (55%) pure 8 as the free. . .

CLM What is claimed is:

. . . (k) washing the extracted fraction with water, drying the fraction, and evaporating it to a crude free base in an **oil** form; (l) dissolving the free base in acidified polar solvent to form a crystalline product.

10. The process of claim 9 wherein the nonpolar solvent of step (b) is mineral **oil**.

L16 ANSWER 16 OF 31 USPATFULL

AB The A21 receptor extracelluar site and the A2 receptor extracellular site of adenosine analogues are structurally different and that binding orientations of adenosine or adenosine analogues are different at these sites and this may be used to determine their structure. Novel pyrimidine compounds are described.

AN 93:57026 USPATFULL

TI Pyrazolo[3,4-d]pyrimidines with adenosine-like binding affinities

IN Quinn, Ronald J., Brisbane, Australia
Dooley, Michael J., Brisbane, Australia
Scammells, Peter J., Brisbane, Australia
Chebib, Mary, Brisbane, Australia

PA Griffith University, Queensland, Australia (non-U.S. corporation)

PI US 5227485 19930713 <--

AI US 1991-717202 19910619 (7)

PRAI AU 1990-691 19900619

DT Utility

FS Granted

EXNAM Primary Examiner: Brown, Johnnie R.; Assistant Examiner: Crane, L. Eric

LREP Nixon & Vanderhye

CLMN Number of Claims: 3

ECL Exemplary Claim: 1,2,3

DRWN 10 Drawing Figure(s); 8 Drawing Page(s)

LN.CNT 673

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5227485 19930713 <--

DETD . . . cells, endocrine gland cells, blood elements and vasculature while A1 receptor sites also occur in brain cells, heart cells and **fat** cells. A2 receptor sites can be classified into low affinity binding sites and high affinity binding sites.

DETD Interestingly, 1-methylisoguanosine can interact with benzodiazepine receptors (Ki of approximately 17 .mu.M vs .sup.3 H-**diazepam** binding, Kd=11 nM), being several hundred fold more potent than inosine and hypoxanthine, two purines which have been suggested as. . .

DETD Like **diazepam**, 1-methylisoquanosine decreases cerebellar levels of cyclic GMP (Davies, Baird Lambert et al above) confirming observations that alterations in behavioural (or. . .

DETD Adenosine may be the brain's natural anticonvulsant. It is involved in the spontaneous arrest of **epileptic seizures** and is brought into play by the seizure itself [Dragunow Trends in Pharm Sci 128-129 (1986)]. NECA displayed slightly more. . .

DETD . . . water (3.times.10 ml), dried over anhydrous magnesium sulphate

for 60 min, filtered and reduced under vacuum to leave a brown **oil** (0.25 g). The **oil** was flash-chromatographed (ethyl acetate-hexane 1-1) on a 3.times.10 cm column and the fractions containing the single product with approximately 0.6. . .

DETD . . . has been shown that adenosine may be the brain's natural anticonvulsant, that adenosine is involved in the spontaneous arrest of **epileptic seizures** and that it is brought into play by the seizure itself. Adenosine agonists have anticonvulsant activity. Adenosine has also been. . .

L16 ANSWER 17 OF 31 USPATFULL

AB The subject compounds, which are adapted for the site-specific/sustained delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D-DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine .revreaction. pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is lower alkyl or benzyl and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH functional group to the carbonyl function of [DHC], then [D] must be other than a sympathetic stimulant, steroid sex hormone or long chain alkanol; and

(b) non-toxic pharmaceutically acceptable salts of compounds of formula (I) wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine .revreaction. pyridinium salt redox carrier. The corresponding ionic pyridinium salt type drug/carrier entities [D-QC].sup.+ X.sup.- are also disclosed.

AN 93:12516 USPATFULL

TI Brain-specific drug delivery

IN Bodor, Nicholas S., Gainesville, FL, United States

PA University of Florida, Gainesville, FL, United States (U.S. corporation)

PI US 5187158 19930216 <--

AI US 1991-639283 19910110 (7)

RLI Division of Ser. No. US 1989-295938, filed on 11 Jan 1989, now patented, Pat. No. US 5008257 which is a division of Ser. No. US 1984-665940, filed on 29 Oct 1984, now patented, Pat. No. US 4824850 which is a continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 And a continuation-in-part of Ser. No. US 1983-461543, filed on 27 Jan 1983, now abandoned And a continuation-in-part of Ser. No. US 1985-733463, filed on 13 May 1985, now patented, Pat. No. US 4727079 And a continuation-in-part of Ser. No. US 1983-475493, filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And a continuation-in-part of Ser. No. US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564

PRAI CA 1983-428192 19830516

DT Utility
FS Granted
EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Turnipseed, James H.
LREP Burns, Doane, Swecker & Mathis
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 6314
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5187158 19930216 <--
SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules such as water and urea may pass through the. . . carrier-mediated and active transport processes govern the movement of many molecules through the BBB. Thus, it is generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .
SUMM . . . in regulating drug concentrations in the CNS. There are several efflux processes: bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartments. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.
DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.
DETD . . . dopamine precursor used, for example, in the treatment of Parkinsonism); muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam and phenothiazine tranquilizers such as carphenazine, fluphenazine and the like; mild and strong analgesics and narcotics; sedatives and. . .
DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)-adenine; 6-azaurinde; idoxuridine; trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers, such as **diazepam**, oxazepam, lorazepam, chlordiazepoxide, flurazepam, bromazepam,

chlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers/anticonvulsants such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . system for dopamine, compound 5, on administration (e.g., by injection) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enter the CNS. Following oxidation both in the brain and in the other. . . quaternary precursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic** derivatization of the catechol system in dopamine has also now been demonstrated.

DETD Accordingly, provided hereby is a potent, brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protective group(s)], which penetrates. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g., the enkephalins, which have been found to initiate **epileptic seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular injection of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionite (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield, 0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very slowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

DETD . . . hr, after which time the precipitate was removed by filtration. Solvents were removed at reduced pressure to give an orange **oil** which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta.[(CD.sub.3).sub.2 CO] 9.7 (bs,. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil**

which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta. (CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4 .multidot.1/2H.sub.2 O: C, 63.16; H,. . .

DETD . . . the solution was warmed to room temperature. After 24 hours, the solvent was removed under reduced pressure. The resulting dark **oil** was triturated with petroleum ether but no solidification occurred. Identity of the product was confirmed by NMR analysis. The product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil** . Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to give an orange **oil** . UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 : C, 64.52; H, 6.45; N,. . .

DETD . . . ether was added and then removed (10.times.5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4. Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1581## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow **oil** which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl acetate left a yellow **oil** which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;. .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1583##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to

a gentle reflux and refluxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange

solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow **oil** reduced methanolic silver nitrate immediately. The structure of the product was confirmed by NMR analysis to be: ##STR1585##

DETD . . . and the solution was stirred for 4 hours. The organic layer was

dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1586##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidinedione (2 g, 0.0071 mol) was dissolved in bromoacetylchloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. C. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yellow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . concentration of the intermediate charged species (quaternary form) in the brain even after one single bolus injection of the starting

lipophilic chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L16 ANSWER 18 OF 31 USPATFULL

AB A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures, comprising systemically administering to said subject a safe and effective amount of a compound of the formula: ##STR1## wherein (a) X is halo or nil, and

Y is a substituent selected from the group consisting of unsubstituted or halogen-substituted methyl, halo, nitro, amino, and methoxy; and

(b) R is R.sup.1 C(O)OH, R.sup.1 C(O)N(R.sup.2).sub.2, or R.sup.1 N(R.sup.2).sub.2 ; where

R.sup.1 is C.sub.1 -C.sub.3 alkylene which is unsubstituted or substituted with C.sub.1 -C.sub.2 alkyl; and

each R.sup.2 is, independently, hydrogen or lower alkyl; or

both R.sup.2 groups are connected to form a saturated 5- or 6-membered heterocycle containing 1 or 2 heteroatoms, wherein one of which is nitrogen and the other is selected from oxygen and nitrogen and said heterocycle is unsubstituted or substituted with lower alkyl or hydroxy-substituted lower alkyl;

or a pharmaceutically-acceptable salt thereof. Preferably X is halo.

AN 92:15052 USPATFULL

TI 5-phenyl-2-furan ketones and use as antiepileptic agents

IN Pelosi, Jr., Stanford S., Norwich, NY, United States

PA Norwich Eaton Pharmaceuticals, Inc., Norwich, NY, United States (U.S. corporation)

PI US 5091426 19920225 <--

AI US 1989-371354 19890623 (7)

DT Utility

FS Granted

EXNAM Primary Examiner: Raymond, Richard L.

LREP Suter, David L., Clark, Karen F., Schaeffer, Jack D.

CLMN Number of Claims: 21

ECL Exemplary Claim: 1,12

DRWN No Drawings

LN.CNT 606

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5091426 19920225 <--

AB A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures, comprising systemically administering to said subject a safe and. . .

SUMM . . . with three quarters of the patients having their first seizure before the age of 18. Two hundred thousand Americans have **epileptic seizures** more than once a month. Most epileptic patients are dependent on drugs to control seizures, but therapy is often inadequate.. . .

SUMM . . . a dormant period lasting for twelve years, from 1961 to 1973, during which the only new drug of interest was **diazepam**, an adjunctive drug used mostly in status epilepticus.

SUMM The present invention encompasses certain 5-phenyl-2-furan ketones and compositions thereof. It also encompasses methods of using these compounds to prevent **epileptic seizures** in a human or lower animal subject susceptible to such seizures. Specifically, the compounds of this invention are of the. . .

SUMM . . . 5-phenyl-2-furan ketones and compositions (hereinafter referred to as "5-phenyl furans"). It also encompasses methods for using these compounds to prevent **epileptic seizures** in a human or other animal susceptible to such seizures. Specific compounds and compositions to be used in the invention. . .

SUMM The present invention also provides compositions for lessening the severity or frequency of **epileptic seizures**, comprising:

SUMM . . . particular, pharmaceutically-acceptable carriers for systemic administration include water, sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable **oils**, synthetic **oils**, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, pyrogen-free water, fixed **oils**, isopropyl myristate, benzyl benzoate, dioxolones, glycofurol, dimethylacetamide, N-(.beta.-hydroxyethyl)-lactamide, ethyl lactate, polyethylene glycols, glycerin, and 1,3 butylene glycol or a mixture. . . aqueous and nonaqueous vehicles that contain or consist of, for example, water, propylene glycol, ethyl oleate, pyrrolidone, ethanol, or sesame **oil**. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

SUMM The present invention also encompasses a method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures which comprises systemically administering to said human or lower. . .

SUMM . . . will be administered once daily. Treatment regimens can extend for the life of the subject depending on the type of **epileptic seizure** to which the subject is susceptible.

SUMM A "safe and effective amount" of a 5-phenyl furan is an amount that is effective to inhibit **epileptic seizures** in a human or lower animal susceptible to said **epileptic seizures**, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit/risk ratio when used. . .

SUMM As used herein, **"epileptic seizures"** refer to changes in behavior or activity caused by an excessive electrical discharge in the brain cells. A susceptibility to. . .

SUMM The International Classification of **Epileptic Seizures** classifies seizures into those that have a partial or focal onset in one area of the brain and those that. . .

DETD . . . and the ether layer is dried over MgSO.sub.4. The solvent is removed on a rotary evaporator to give a residual **oil**. The **oil** is dissolved in anhydrous ether and is treated with ethereal HCl. The solid is collected by filtration and is dissolved. . .

DETD . . . acid. The ether layer is then separated, dried over MgSO.sub.4 and concentrated on a rotary evaporator to yield a residual **oil**. This **oil** is extracted with refluxing hexane and the hexane upon cooling yields 12.5 g (27%) of product. An analytical sample is.

.

CLM What is claimed:

12. A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures, comprising systemically administering to said subject a safe and. . .

13. A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures, according to claim 12 wherein X is nil.

14. A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures, according to claim 12 wherein X is halo.

15. A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures, according to claim 12 wherein Y is halosubstituted methyl. . . .

16. A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures, according to claim 15 wherein Y is trifluoromethyl.

17. A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures, according to claim 12 wherein R is R.sup.1 C(O)OH. . .

18. A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures, according to claim 12 wherein R is R.sup.1 C(O)N(R.sup.2).sub.2,. . .

19. A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures, according to

claim 12 wherein X is nil, R. . .
20. A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures according to claim 14 wherein R is 3-diethylamino-2,2-dimethylpropyl and. . .
21. A method of preventing **epileptic seizures** in a human or lower animal subject susceptible to said seizures according to claim 15 wherein Y is selected from. . .

L16 ANSWER 19 OF 31 USPATFULL
AB A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures, comprising systemically administering to said subject a safe and effective amount of a compound of the formula: ##STR1## wherein (a) X is halo or hydrogen, and Y is a substituent selected from the group consisting of unsubstituted or halogen-substituted methyl, halo, nitro, amino, and methoxy; and

(b) R is N(R.sup.3).sub.2, OR.sup.1 N(R.sup.3).sub.2, N(R.sup.2)R.sup.1 N(R.sup.3).sub.2, or N(R.sup.2)N(R.sup.3).sub.2 ; where

R.sup.1 is C.sub.1 -C.sub.3 alkylene which is unsubstituted or substituted with C.sub.1 -C.sub.2 alkyl;

R.sup.2 is hydrogen or lower alkyl; and

each R.sup.3 is, independently, hydrogen or lower alkyl; or both R.sup.3 groups are connected to form a saturated 5- or 6-membered heterocycle containing 1 or 2 heteroatoms selected from oxygen and nitrogen and said heterocycle is unsubstituted or substituted with lower alkyl or hydroxy-substituted lower alkyl;

or a pharmaceutically-acceptable salt thereof.

Preferably X is halo, preferably Y is trifluoromethyl, and R is preferably 3-diethylamino-2,2-dimethylpropoxy.
AN 91:46731 USPATFULL
TI Use of 5-phenyl-2-furan esters and amides as antiepileptic agents
IN Burch, Homer A., Norwich, NY, United States
Castellion, Alan W., Oxford, NY, United States
Pelosi, Jr., Stanford S., Norwich, NY, United States
PA Norwich Eaton Pharmaceuticals, Inc., Norwich, NY, United States (U.S. corporation)
PI US 5023272 19910611 <--
AI US 1989-371355 19890623 (7)
DT Utility
FS Granted
EXNAM Primary Examiner: Shah, Mukund J.; Assistant Examiner: Datlow, Philip I.
LREP Suter, David L., Clark, Karen F., Schaeffer, Jack D.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 774
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5023272 19910611 <--
AB A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures, comprising systemically administering to said subject a safe and effective. . .
SUMM . . . with three quarters of the patients having their first seizure

before the age of 18. Two hundred thousand Americans have **epileptic seizures** more than once a month. Most epileptic patients are dependent on drugs to control seizures, but therapy is often inadequate.. . .

SUMM . . . a dormant period lasting for twelve years, from 1961 to 1973, during which the only new drug of interest was **diazepam**, an adjunctive drug used mostly in status epilepticus.

SUMM The present invention encompasses certain novel 5-phenyl-2-furan esters and amides and compositions thereof. It also encompasses methods for preventing **epileptic seizures** in a human or other mammal susceptible to such seizures, using these compounds and related compounds. These methods comprise systemically. . .

SUMM . . . encompasses certain novel 5-phenyl-2-furan esters and amides and compositions using these and related compounds. It also encompasses methods for preventing **epileptic seizures** in a human or mammal subject susceptible to such seizures, using these compounds and related compounds. Specific compounds and compositions. . .

SUMM The present invention encompasses a method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures which comprises systemically administering to said subject a safe and. . .

SUMM . . . will be administered once daily. Treatment regimens can extend for the life of the subject depending upon the type of **epileptic seizure** to which the subject is susceptible.

SUMM A "safe and effective amount" of a 5-phenyl furan is an amount that is effective to inhibit **epileptic seizures** in a human or mammal subject susceptible to said **epileptic seizures**, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit/risk ratio when used. . .

SUMM As used herein, "**epileptic seizures**" refer to changes in behavior or activity caused by an excessive electrical discharge in the brain cells. A susceptibility to. . .

SUMM The International Classification of **Epileptic Seizures** classifies seizures into those that have a partial or focal onset in one area of the brain and those that. . .

SUMM The present invention also provides compositions for lessening the severity or frequency of **epileptic seizures**, comprising:

SUMM . . . particular, pharmaceutically-acceptable carriers for systemic administration include water, sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable **oils**, synthetic **oils**, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, pyrogen-free water, fixed **oils**, isopropyl myristate, benzyl benzoate, dioxolones, glycofurol, dimethylacetamide, N-(.beta.-hydroxyethyl)-lactamide, ethyl lactate, polyethylene glycols, glycerin, 1,3 butylene glycol or a mixture of. . . Preferred carriers for parenteral administration include aqueous and non-aqueous vehicles containing water, propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame **oil** and mixtures thereof. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of. . .

DETD . . . H.sub.2 O (50 ml.), is dried over MgSO.sub.4, is filtered, and is concentrated to dryness under reduced pressure. The resultant **oil** (30 ml.) is treated with 10% HCl (280 ml.) and is subjected to steam distillation for 1.3 hours, collecting 1. . . cold, is extracted with ether, is dried over MgSO.sub.4 and activated charcoal, is filtered, and concentrated to dryness. The residual **oil** (12

g. plus 5.0 g. from previous run) is distilled at 60.degree.-68.degree./1 mm to yield 11 g (35%) of 3-diethylamino-2,2-diethylpropanol.

DETD . . . over MgSO.sub.4 and the solvent is then removed on a rotary evaporator to yield the free base as a residual **oil**. This **oil**, 3.5 g. (0.035 mole) of triethylamine, and 75 ml. of toluene is heated to 80.degree.. At a temperature of 75.degree.-80.degree.. . . of solid is filtered and discarded. The filtrate is taken to dryness on a rotary evaporator to yield a residual **oil**. This **oil** is triturated in ethyl acetate with a solid forming. The solid is filtered and is air dried to yield 10.5. . .

CLM What is claimed is:

1. A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures, comprising systemically administering to said subject a safe and effective. . .

2. A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures, according to claim 1 wherein X is hydrogen.

3. A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures, according to claim 1 wherein X is halo.

4. A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures, according to claim 1 wherein Y is halosubstituted methyl.

5. A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures, according to claim 1 wherein Y is trifluoromethyl.

6. A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures, according to claim 1 wherein R is N(R.sup.3).sub.2, N(R.sup.2)R.sup.1 N(R.sup.3).sub.2. . .

7. A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures, according to claim 1 wherein R is OR.sup.1 N(R.sup.3).sub.2.

8. A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures, according to claim 2, wherein R is 3-diethylamino-2,2-dimethylpropoxy and Y. . .

9. A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures according to claim 3 wherein R is 3-diethylamino-2,2-dimethylpropoxy and X. . .

10. A method of preventing **epileptic seizures** in a human or mammal susceptible to said seizures according to claim 8 wherein Y is selected from the group. . .

11. A method of preventing **epileptic seizures** in a human or mammal subject susceptible to said seizures, comprising systemically administering to said subject a safe and effective. . .

L16 ANSWER 20 OF 31 USPATFULL
AB The subject compounds, which are adapted for the site-specific/sustained
delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D-DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of
a dihydropyridine.revreaction.pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is a lower alkyl or benzyl
and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH functional group to the carbonyl function of [DHC], then [D] must be other than a sympathetic stimulant, steroid sex hormone or long chain alkanol; and

(b) non-toxic pharmaceutically acceptable salts of compounds of formula (I) wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of
a dihydropyridine.revreaction.pyridinium salt redox carrier. The corresponding ionic pyridinium salt type drug/carrier entities [D-QC].sup.+ X.sup.- are also disclosed.
AN 91:30479 USPATFULL
TI Brain-specific drug delivery
IN Bodor, Nicholas S., Gainesville, FL, United States
PA University of Florida, Gainesville, FL, United States (U.S. corporation)
PI US 5008257 19910416 <--
AI US 1989-295938 19890111 (7)
RLI Division of Ser. No. US 1984-665940, filed on 29 Oct 1984, now patented,
Pat. No. US 4824850 which is a continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 Ser. No. Ser. No. US 1983-461543, filed on 27 Jan 1983, now abandoned Ser. No. Ser. No. US 1985-733463, filed on 13 May 1985, now patented, Pat. No. US 4622218 Ser. No. Ser. No. US 1983-475493, filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And Ser. No. US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564
PRAI CA 1983-428192 19830516
DT Utility
FS Granted
EXNAM Primary Examiner: Stoll, Robert L.; Assistant Examiner: Covert, John M.
LREP Baumeister, Mary Katherine
CLMN Number of Claims: 28
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 6383
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5008257 19910416 <--
SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB

is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules such as water and urea may pass through the. . . carrier-mediated and active transport processes govern the movement of many molecules through the BBB. Thus, it is generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .

SUMM . . . in regulating drug concentrations in the CNS. There are several efflux processes bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.

DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.

DETD . . . dopamine precursor used, for example, in the treatment of Parkinsonism); muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam and phenothiazine tranquilizers such as carphenazine, fluphenazine and the like; mild and strong analgesics and narcotics; sedatives and. . .

DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)adenine; 6-azauridine; idoxuridine; trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers, such as **diazepam**, oxazepam, lorazepam, chlordiazepoxide, flurazepam, bromazepam, chlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers/anti-convulsants such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . system for dopamine, compound 5, on administration (e.g., by injection) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enters the CNS. Following oxidation both in the brain and in the other. . . quaternary precursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic** derivatization of the catechol system in dopamine has also now been demonstrated.

DETD Accordingly, provided hereby is a potent, brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type

chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug"
in the case of the catechol protective group(s)], which penetrates. . .

DETD 2. **Diazepam**: ##STR44## This reaction scheme utilizes conventional opening of the 7-member ring, accompanied by coupling of the drug to the carrier.. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g., the
enkephalins, which have been found to initiate **epileptic seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular injection of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionite (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . iodide, 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield,0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very slowly U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..
. .

DETD . . . hr, after which time the precipitate was removed by filtration.
Solvents were removed at reduced pressure to give an orange **oil** which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta. [(CD.sub.3).sub.2 CO] 9.7. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta. (CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4.
1/2H.sub.2 O: C, 63.16; H,. . .

DETD . . . the solution was warmed to room temperature. After 24 hours,

the solvent was removed under reduced pressure. The resulting dark **oil** was triturated with petroleum ether but no solidification occurred. Identity of the product was confirmed by NMR analysis. The product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil** . Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to give an orange **oil** . UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 : C, 64.52; H, 6.45; N,. . .

DETD . . . ether was added and then removed (10.times.5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4. Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1506## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow **oil** which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl aetate left a yellow **oil** which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;. .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1508##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to a gentle reflux and relfuxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow **oil** reduced methanolic silver nitrate immediately. The structure of the product was confirmed by NMR analysis to be: ##STR1510##

DETD . . . and the solution was stirred for 4 hours. The organic layer was

dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1511##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidinedione (2 g, 0.0071 mol) was dissolved in bromoacetylchloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. C. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yellow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . concentration of the intermediate charged species (quaternary form) in the brain even after one single bolus injection of the starting **lipophilic** chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L16 ANSWER 21 OF 31 USPATFULL

AB The subject compounds, which are adapted for the site-specific/sustained delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D--DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine.revreaction.pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is lower alkyl or benzyl and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH function group to the carbonyl function of [DHC], then [D] must be other than a sympathetic stimulant, steroid sex hormone or long chain alkanol; and

(b) non-toxic pharmaceutically acceptable salts of compounds of formula (I) wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine.revreaction.pyridinium salt redox carrier. The corresponding ionic pyridinium salt type drug/carrier entitles [D--QC].sup.+ X.sup.- are also disclosed.

AN 90:11422 USPATFULL

TI Brain-specific drug delivery of steroid sex hormones cleaved from pyridinium carboxylates and dihydro-pyridine carboxylate precursors

IN Bodor, Nicholas S., Gainesville, FL, United States

PA University of Florida, Gainesville, FL, United States (U.S. corporation)

PI US 4900837 19900213 <--
AI US 1987-76191 19870721 (7)
DCD 20020910
RLI Division of Ser. No. US 1984-665940, filed on 29 Oct 1984, now patented,
Pat. No. US 4824850 which is a continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 And
a continuation-in-part of Ser. No. US 1983-461543, filed on 27 Jan 1983,
now abandoned And a continuation-in-part of Ser. No. US 1983-475493, filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And a continuation-in-part of Ser. No. US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564
PRAI JP 1982-101940 19820614
CA 1983-428192 19830516
IE 1983-1149 19830517
ZA 1983-3521 19830517
ES 1983-522489 19830517
IT 1983-48327 19830518
DT Utility
FS Granted
EXNAM Primary Examiner: Rotman, Alan R.
LREP Baumeister, Mary Katherine, Clarke, Dennis P.
CLMN Number of Claims: 41
ECL Exemplary Claim: 1,27
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 6389
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4900837 19900213 <--
SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such
a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules
such as water and urea may pass through the. . . carrier-mediated and
active transport processes govern the movement of many molecules through
the BBB. Thus, it is generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary
combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .
SUMM . . . in regulating drug concentrations in the CNS. There are several
efflux processes: bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted

that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.

DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.

DETD . . . dopamine precursor used, for example, in the treatment of Parkinsonism); muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam and phenothiazine tranquilizers such as carphenazine, fluphenazine and the like; mild and strong analgesics and narcotics; sedatives and. . .

DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)adenine; 6-azauridine; idoxuridine; trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers, such as **diazepam**, oxazepam, lorazepam, chloridazepoxide, flurazepam, bromazepam, chlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers/anticonvulsants such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . system for dopamine, compound 5, on administratio (e.g., by injection) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enters the CNS. Following oxidation both in the brain and in the other. . . quaternary precursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic** derivatization of the catechol system in dopamine has also now been demonstrated.

DETD Accordingly, provided hereby is a potent, brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protectiv group(s)], which penetrates. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g, the enkephalins, which have been found to initiate **epileptic**, **seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular injection of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionate (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield, 0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very sowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over

Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

. .

DETD . . . hr, after which time the precipitate was removed by filtration.

Solvents were removed at reduced pressure to give an orange **oil** which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta.[(CD.sub.3).sub.2 CO] 9.7 (bs,. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta.(CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine 4-5+C--H);. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4.1/2H.sub.2 O: C, 63.16; H, 5.88;. . .

DETD . . . the solution was warmed to room temperature. After 24 hours, the solvent was removed under reduced pressure. The resulting dark **oil** was triturated with petroleum ether but no solidification occurred. Identity of the product was confirmed by NMR analysis. The product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil** . Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to given an orange **oil**. UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 O: C, 64.52; H, 6.45; N,. . .

DETD . . . MgSO.sub.4. The ether layer was decanted from the drying agent and the solvent was removed under reduced pressure. To the **oil** residue, ether was added and then removed (10.times.5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4. Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1569## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow

oil which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl aetate left a yellow **oil** which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;. . .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1571##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to a gentle reflux and refluxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow **oil** reduced methanolic silver nitrate immediately. The structure of the product was confirmed by NMR analysis to be: ##STR1573##

DETD . . . and the solution was stirred for 4 hours. The organic layer was dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1574##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidinedione (2 g, 0.0071 mol) was dissolved in bromoacetylchloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. c. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yelllow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . concentration of the intermediate charged species (quarternary form) in the brain even after one single bolus injection of the starting **lipophilic** chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L16 ANSWER 22 OF 31 USPATFULL

AB The subject compounds, which are adapted for the site-specific/sustained

delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D--DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine .revreaction. pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is lower alkyl or benzyl and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH functional group to the carbonyl function of [DHC], then [D] must be other than a sympathetic stimulant, steroid sex hormone or long chain alkanol; and

(b) non-boxic pharmaceutically acceptable salts of compounds of formula (I) wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine .revreaction. pyridinium salt redox carrier. The corresponding ionic pyridinium salt type drug/carrier entities [D--QC].sup.+ X.sup.- are also disclosed.

AN 89:92627 USPATFULL
TI Brain-specific drug delivery
IN Bodor, Nicholas S., Gainesville, FL, United States
PA University of Florida, Gainesville, FL, United States (U.S. corporation)
PI US 4880921 19891114 <--
AI US 1987-75830 19870720 (7)
DCD 20020910
RLI Division of Ser. No. US 1984-665940, filed on 29 Oct 1984, now patented, Pat. No. US 4824850 which is a continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 And a continuation-in-part of Ser. No. US 1983-461543, filed on 27 Jan 1983, now abandoned And a continuation-in-part of Ser. No. US 1983-475493, filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And a continuation-in-part of Ser. No. US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564
PRAI JP 1982-101940 19820614
CA 1983-428192 19830516
IE 1983-1149 19830517
ZA 1983-3521 19830517
ES 1983-522489 19830517
IT 1983-48327 19830518
DT Utility
FS Granted
EXNAM Primary Examiner: Robinson, Douglas W.; Assistant Examiner: Lipovsky, Joseph A.
LREP Baumeister, Mary Katherine, Clarke, Dennis P.
CLMN Number of Claims: 54
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 6386
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 4880921 19891114 <--
SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules such as water and urea may pass through the. . . carrier-mediated and active transport processes govern the movement of many molecules through the BBB. Thus, it is generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .

SUMM . . . in regulating drug concentrations in the CNS. There are several efflux processes: bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.

DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.

DETD . . . dopamine precursor used, for example, in the treatment of Parkinsonism); muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam and phenothiazine tranquilizers such as carphenazine, fluphenazine and the like; mild and strong analgesics and narcotics; sedatives and. . .

DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)-adenine; 6-azauridine; idoxuridine; trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers, such as **diazepam**, oxazepam, lorazepam, chlordiazepoxide, flurazepam, bromazepam, chlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers/anticonvulsants such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . system for dopamine, compound 5, on administration (e.g., by injection) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enters the CNS. Following oxidation both in the brain and in the other. . . quaternary percursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic** derivatization of the

catechol system in dopamine has also now been demonstrated.

DETD Accordingly, provided hereby is a potent brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protective group(s)], which penetrates. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g., the enkephalins, which have been found to initiate **epileptic seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular injection of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionite (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield, 0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very slowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

DETD . . . hr, after which time the precipitate was removed by filtration. Solvents were removed at reduced pressure to give an orange **oil** which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta.[(CD.sub.3).sub.2 CO] 9.7 (bs,. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta. (CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4.1/2H.sub.2 O: C, 63.16; H, 5.88;. . .

DETD . . . the solution was warmed to room temperature. After 24 hours, the solvent was removed under reduced pressure. The resulting dark

oil was triturated with petroleum ether but no solidification occurred. Identity of the product was confirmed by NMR analysis. The product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil** . Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to give an orange **oil** . UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 : C, 64.52; H, 6.45; N,. . .

DETD . . . ether was added and then removed (10.times.5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4. Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1499## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow **oil** which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl aetate left a yellow **oil** which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;. . .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1501##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to a gentle reflux and relfuxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow **oil** reduced methanolic silver nitrate immediately. The structure of the product was confirmed by NMR analysis to be: ##STR1503##

DETD . . . and the solution was stirred for 4 hours. The organic layer was

dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1504##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidinedione (2 g, 0.0071 mol) was dissolved in bromoacetylchloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. C. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yellow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . concentration of the intermediate charged species (quaternary form) in the brain even after one single bolus injection of the starting **lipophilic** chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L16 ANSWER 23 OF 31 USPATFULL

AB The subject compounds, which are adapted for the site-specific/sustained delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D--DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine.revreaction.pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is lower alkyl or benzyl and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH function group to the carbonyl function of [DHC], then [D] must be other than a sympathetic stimulant, steroid sex hormone or long chain alkanol; and

(b) non-toxic pharmaceutically acceptable salts of compounds of formula (I) wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine.revreaction.pyridinium salt redox carrier. The corresponding ionic pyridinium salt type drug/carrier entitles [D--QC].sup.+ X.sup.- are also disclosed.

AN 89:32284 USPATFULL

TI Brain-specific drug delivery

IN Bodor, Nicholas S., Gainesville, FL, United States

PA University of Florida, Gainesville, FL, United States (U.S. corporation)

PI US 4824850 19890425 <--
AI US 1984-665940 19841029 (6)
RLI Continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 And a continuation-in-part of Ser. No.
US 1983-461543, filed on 27 Jan 1983, now abandoned And a continuation-in-part of Ser. No. US 1983-475493, filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And a continuation-in-part of Ser. No.
US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564
PRAI CA 1983-428192 19830516
DT Utility
FS Granted
EXNAM Primary Examiner: Gron, Teddy S.; Assistant Examiner: Thomas, J. E.
LREP Baumeister, Mary Katherine, Clarke, Dennis P.
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 6396
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4824850 19890425 <--
SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules such as water and urea may pass through the. . . carrier-mediated and active transport processes govern the movement of many molecules through the BBB. Thus, it is generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .
SUMM . . . in regulating drug concentrations in the CNS. There are several efflux processes: bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.
DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.
DETD . . . dopamine precursor used, for example, in the treatment of Parkinsonism); muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and

oxazepam and phenothiazine tranquilizers such as carphenazine, fluphenazine and the like; mild and strong analgesics and narcotics; sedatives and. . .

DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)adenine; 6-azauridine; idoxuridine; trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers, such as **diazepam**, oxazepam, lorazepam, chloridazepoxide, flurazepam, bromazepam, chlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers/anticonvulsants such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . system for dopamine, compound 5, on administratio (e.g., by injection) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enters the CNS. Following oxidation both in the brain and in the other. . . quaternary precursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic** derivatization of the catechol system in dopamine has also now been demonstrated.

DETD Accordingly, provided hereby is a potent, brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protectiv group(s)], which penetrates. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g, the enkephalins, which have been found to initiate **epileptic**, **seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular injection of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionate (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield, 0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very sowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

. .

DETD . . . hr, after which time the precipitate was removed by filtration.

Solvents were removed at reduced pressure to give an orange **oil**

which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta.[(CD.sub.3).sub.2 CO] 9.7 (bs,. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta.(CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine 4-5+C--H);. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4.1/2H.sub.2 O: C, 63.16; H, 5.88;. . .

DETD . . . the solution was warmed to room temperature. After 24 hours, the solvent was removed under reduced pressure. The resulting dark **oil** was triturated with petroleum ether but no solidification occurred. Identity of the product was confirmed by NMR analysis. The product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil** . Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to given an orange **oil**. UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 O: C, 64.52; H, 6.45; N,. . .

DETD . . . MgSO.sub.4. The ether layer was decanted from the drying agent and the solvent was removed under reduced pressure. To the **oil** residue, ether was added and then removed (10 times 5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4. Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1569## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow **oil** which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl aetate left a yellow **oil** which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white

precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;. . .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1571##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to a gentle reflux and refluxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow **oil** reduced methanolic silver nitrate immediately. The structure of the product was confirmed by NMR analysis to be: ##STR1573##

DETD . . . and the solution was stirred for 4 hours. The organic layer was dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1574##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidinedione (2 g, 0.0071 mol) was dissolved in bromoacetylchloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. c. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yelllow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . concentration of the intermediate charged species (quarternary form) in the brain even after one single bolus injection of the starting **lipophilic** chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L16 ANSWER 24 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AB This report concerns three patients in whom continuous intravenous infusion of Diazemuls (**diazepam** dissolved in soya bean **oil** and emulsified) diluted in 5.5% glucose was used for the controlling of **epileptic seizures** (status). Diazemuls infusion was effective in one patient with complex partial status epilepticus; in another patient with convulsion secondary to a brain stem infarct, the convulsions were abolished; while only reduced jerking was achieved in the third patient suffering from myoclonic jerks caused by anoxic brain damage. Infusion time ranged from 15 to 33 h. The serum concentrations of **diazepam** obtained during the infusions were higher than recommended in the literature for treatment of status

epilepticus, but could not be correlated to either clinical efficacy or infusion rate.

AN 1987:445734 BIOSIS
DN BA84:101572
TI INTRAVENOUS INFUSION OF DIAZEMULS IN THE CONTROL OF STATUS-LIKE **EPILEPTIC SEIZURES** OF DIFFERENT ETIOLOGY.
AU HOGSKILDE S; SORENSEN S P S; THISTED B; SORENSEN M B
CS DEP. ANESTHESIOL. INTENSIVE CARE, COPENHAGEN MUNICIPAL HOSP., OSTER FARIMAGSGADE 5, DK-1399 COPENHAGEN K, DENMARK.
SO ACTA ANAESTHESIOL SCAND, (1987) 31 (6), 506-508.
CODEN: AANEAB. ISSN: 0001-5172.
FS BA; OLD
LA English
TI INTRAVENOUS INFUSION OF DIAZEMULS IN THE CONTROL OF STATUS-LIKE **EPILEPTIC SEIZURES** OF DIFFERENT ETIOLOGY.
SO ACTA ANAESTHESIOL SCAND, (1987) 31 (6), 506-508.
CODEN: AANEAB. ISSN: 0001-5172.
AB This report concerns three patients in whom continuous intravenous infusion of Diazemuls (**diazepam** dissolved in soya bean **oil** and emulsified) diluted in 5.5% glucose was used for the controlling of **epileptic seizures** (status). Diazemuls infusion was effective in one patient with complex partial status epilepticus; in another patient with convulsion secondary to. . . from myoclonic jerks caused by anoxic brain damage. Infusion time ranged from 15 to 33 h. The serum concentrations of **diazepam** obtained during the infusions were higher than recommended in the literature for treatment of status epilepticus, but could not be. . .

L16 ANSWER 25 OF 31 USPATFULL
AB The subject compounds, which are adapted for the site-specific/sustained delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D-DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine .revreaction. pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is lower alkyl or benzyl and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH functional group to the carbonyl function of [DHC], then [D] must be other than a sympathetic stimulant, steroid sex hormone or long chain alkanol; and

(b) non-toxic pharmaceutically acceptable salts of compounds of formula (I) wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine .revreaction. pyridinium salt redox carrier. The corresponding ionic pyridinium salt type drug/carrier entities [D-QC].sup.+ Y.sup.- are also disclosed.

AN 85:53658 USPATFULL
TI Brain-specific drug delivery
IN Bodor, Nicholas S., Gainesville, FL, United States

PA University of Florida, Gainesville, FL, United States (U.S. corporation)
PI US 4540564 19850910 <--
AI US 1983-516382 19830722 (6)
RLI Continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 Ser. No. Ser. No. US 1983-461543, filed on 27 Jan 1983 And Ser. No. US 1983-475493, filed on 15 Mar 1983 ,
said Ser. No. 461543 And Ser. No. 475493 , each which is a continuation-in-part of Ser. No. 379316
PRAI WO 1983-WO725 19830512
CA 1983-428192 19830516
DT Utility
FS Granted
EXNAM Primary Examiner: Nucker, Christine M.
LREP Clarke, Dennis P.
CLMN Number of Claims: 86
ECL Exemplary Claim: 1,12
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 4240
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4540564 19850910 <--
SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such
a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules
such as water and urea may pass through the. . . carrier-mediated and
active transport processes govern the movement of many molecules through
the BBB. Thus, it is generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary
combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .
SUMM . . . in regulating drug concentrations in the CNS. There are several
efflux processes: bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.
DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.
DETD . . . agents, whether sympathetic or parasympathetic, e.g., phenylethylamine, dopamine, tyramine, L-DOPA, muscle relaxants,

tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam, phenothiazine tranquilizers such as carphenazine, fluphenazine and the like, mild and strong analgesics and narcotics, sedatives and hypnotics,. . .

DETD . . . as phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)adenine; 6-azauridine; indoxuridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers such as **diazepam**, oxazepam, lorazepam, chlordiazepoxide, flurazepam, bromazepam, chlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . system for dopamine, compound 5, on administration (e.g., by injection) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enters the CNS. Following oxidation both in the brain and in the other. . . quaternary precursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic** derivatization of the catechol system in dopamine has also now been demonstrated.

DETD Accordingly, provided hereby is a potent, brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protective group(s)], which penetrates. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g., the enkephalins, which have been found to initiate **epileptic seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular injection of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . . .

DETD . . . dithionite (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield, 0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very slowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

DETD . . . hr, after which time the precipitate was removed by filtration.

Solvents were removed at reduced pressure to give an orange **oil** which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta.[(CD.sub.3).sub.2 CO] 9.7 (bs,. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta.(CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine 4-5+C-H);. . .

DETD . . . concentration of the intermediate charged species (quaternary form) in the brain even after one single bolus injection of the starting **lipophilic** chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L16 ANSWER 26 OF 31 USPATFULL

AB Centrally acting drug species are site-specifically/sustainedly delivered to the brain by administering to a patient in need of such treatment a therapeutically effective amount of the target drug species [D] tethered to a reduced, blood-brain barrier penetrating lipoidal form [D-DHC] of a dihydropyridine.revreaction.pyridinium salt type redox carrier. Oxidation of the dihydropyridine carrier moiety in vivo to the ionic pyridinium salt type drug/carrier entity [D-QC].sup.+ prevents elimination thereof from the brain, while elimination from the general circulation is accelerated, and subsequent cleavage of the quaternary carrier/drug species results in sustained delivery of the drug [D] in the brain and facile elimination of the carrier moiety [QC].sup.+.

AN 84:60884 USPATFULL

TI Brain-specific drug delivery

IN Bodor, Nicholas S., Gainesville, FL, United States

PA University of Florida, Gainesville, FL, United States (U.S. corporation)

PI US 4479932 19841030 <--

AI US 1982-379316 19820518 (6)

DT Utility

FS Granted

EXNAM Primary Examiner: Nucker, Christine M.

LREP Clarke, Dennis P.

CLMN Number of Claims: 25

ECL Exemplary Claim: 8,23

DRWN 6 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 1732

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 4479932 19841030 <--

SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules such as water and urea may pass through the. . . carrier-mediated and

active transport processes govern the movement of many molecules through the BBB. Thus, it is generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .

SUMM . . . in regulating drug concentrations in the CNS. There are several efflux processes: bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.

SUMM . . . agents, whether sympathetic or parasympathetic, e.g., phenylethylamine, dopamine, tyramine, L-DOPA, muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam, mild and strong analgesics and narcotics, sedatives and hypnotics, narcotic antagonists, vascular agents, stimulants, anesthetics, small peptides, such. . .

SUMM . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g., the enkephalins which have been found to initiate **epileptic seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionite (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta.7.2 (s,. . .

DETD . . . 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield, 0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very slowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD . . . washed with water, dried with anhydrous Na.sub.2 SO.sub.4 and evaporated on rotavap. Yield, 0.36 g (54%) of a yellow, viscous **oil** which gave green color with ferric chloride test and reduced alcoholic AgNO.sub.3 instantly. U.V. (CH.sub.3 OH) 220 and 360 nm.

L16 ANSWER 27 OF 31 USPATFULL

AB An orally administered pharmaceutical formulation comprising a solid dosage form containing an aliphatic amino acid compound in which the carboxylic acid and primary amine are separated by three or four units. Administered in an acid pH range, the formulation is useful in the treatment of convulsive disorders and also has anxiolytic and sedative properties.

AN 83:6900 USPATFULL
TI Anticonvulsive compositions and method of treating convulsive disorders
IN Fish, Irving, Tenafly, NJ, United States
Schwartz, Stephen A., Bronx, NY, United States
Samuels, Stanley, White Plains, NY, United States
PA New York University, New York, NY, United States (U.S. corporation)
PI US 4372974 19830208 <--
AI US 1981-269629 19810602 (6)
DCD 19990330
RLI Continuation-in-part of Ser. No. US 1980-162907, filed on 25 Jun 1980, now patented, Pat. No. US 4322440
DT Utility
FS Granted
EXNAM Primary Examiner: Friedman, Stanley J.
LREP Darby & Darby
CLMN Number of Claims: 38
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 813
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4372974 19830208 <--
SUMM Accordingly, it is an object of the present invention to provide a method of preventing seizures, and particularly **epileptic seizures** in mammals.
SUMM . . . bases that can be used to prepare suppositories according to the present invention are cocoa butter, glycerinated gelatin, hydrogenated vegetable **oils**, mixtures of polyethylene glycols of various molecular weights, and fatty acid esters of polyethylene glycol. Rectal suppositories for adults are. . .
DETD . . . ether. The post-extraction residue is brought to between pH 5-6
with 2 N HCl extracted with chloroform to give an **oil** bp. 70.degree.-80.degree. C. (4 mm), 7-8% yield. This product N-hydroxy-6-methyl-2-piperidone, is reduced with hydrogen over 10% palladium-charcoal to a lactam,. . .
DETD . . . experience with prior art anticonvulsant agents, which indicates that many of them have dual roles as anxiolytics and sedatives
(e.g., **diazepam** is a sedative, an anxiolytic and an anticonvulsant; phenobarbitol is a sedative, an anxiolytic, and an anticonvulsant). Thus, it is. . .
CLM What is claimed is:
~~15. A method of inhibiting~~ **epileptic seizures** in a patient afflicted with epilepsy which comprises administering to a patient in need of such treatment and prior to the onset of said **epileptic seizure** a composition comprising a coated solid dosage form, said solid dosage form comprising a pharmaceutical formulation including an effective amount. . .

L16 ANSWER 28 OF 31 USPATFULL
AB A pharmaceutical formulation comprising aliphatic amino acid compounds in which the carboxylic acid and primary amine are separated by three or
four units. The compositions are useful in the treatment of convulsive disorders and also have anxiolytic and sedative properties.
AN 82:15037 USPATFULL
TI Anticonvulsive compositions and method of treating convulsive disorders
IN Fish, Irving, Tenafly, NJ, United States
Schwartz, Stephen A., Bronx, NY, United States
Samuels, Stanley, White Plains, NY, United States

PA New York University, New York, NY, United States (U.S. corporation)
PI US 4322440 19820330 <--
AI US 1980-162907 19800625 (6)
DT Utility
FS Granted
EXNAM Primary Examiner: Friedman, Stanley J.
LREP Darby & Darby
CLMN Number of Claims: 36
ECL Exemplary Claim: 27
DRWN No Drawings
LN.CNT 661
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4322440 19820330 <--
SUMM Accordingly, it is an object of the present invention to provide a method of preventing seizures, and particularly **epileptic seizures** in mammals.
SUMM . . . bases that can be used to prepare suppositories according to the present invention are cocoa butter, glycerinated gelatin, hydrogenated vegetable **oils**, mixtures of polyethylene glycols of various molecular weights, and fatty acid esters of polyethylene glycol. Rectal suppositories for adults are. . .
DETD . . . The post-extraction residue is brought to between pH 5-6 with 2
N HCl and extracted with chloroform to give an **oil** bp. 70.degree.-80.degree. C. (4 mm), 7-8% yield. This product N-hydroxy-6-methyl-2-piperidone, is reduced with hydrogen over 10% palladium-charcoal to a lactam,. . .
DETD . . . experience with prior art anticonvulsant agents, which indicates that many of them have dual roles as anxiolytics and sedatives
(e.g., **diazepam** is a sedative, an anxiolytic and an anticonvulsant; phenobarbitol is a sedative, an anxiolytic, and an anticonvulsant). Thus, it is. . .

L16 ANSWER 29 OF 31 USPATFULL
AB 2-Ketoalkyl-4(3H)-quinazolinones of the formula ##STR1## wherein R.sub.1
is an aliphatic, cycloaliphatic or hydrocarbon aromatic group of 1-10 carbon atoms;

A is divalent alkylene of 1 to 10 carbon atoms;

R.sub.2 is an aliphatic, cycloaliphatic, hydrocarbon aromatic or heterocyclic group of 1-10 carbon atoms formed by condensing an acyl ester of the formula R.sub.2 COOR' which can be dissociated to form --COR.sub.2 and R'OH in which R' is the alcoholic portion of said ester;
and

R.sub.3 and R.sub.4 are each hydrogen, hydroxy, amino, halogen, trifluoromethyl, alkyl, alkoxy, alkylthio or alkylsulfonyl each of 1-4 carbon atoms, the substituents other than hydrogen when present being preferably in the 6- and/or 7-position of the quinazolinone nucleus

provide compounds having useful activity as CNS depressants and anticonvulsants. A process is provided for preparing such compounds by ester condensation of a corresponding 2-alkyl-3-substituted-4(3H) quinazolinone with a condensable ester and excess sodium hydride in the presence of a strong ionization solvent such as refluxing 1,2-dimethoxyethane.

AN 80:3268 USPATFULL
TI 2-Ketoalkyl-4(3H)-quinazolinones
IN Wolfe, James F., Blacksburg, VA, United States
Rathman, Terry L., Hershey, PA, United States
PA Research Corporation, New York, NY, United States (U.S. corporation)
PI US 4183931 19800115 <--
AI US 1977-831446 19770908 (5)
DT Utility
FS Granted
EXNAM Primary Examiner: Coughlan, Jr., Paul M.
LREP Haight & Huard
CLMN Number of Claims: 17
ECL Exemplary Claim: 4,8
DRWN No Drawings
LN.CNT 1822
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4183931 19800115 <--
SUMM . . . while protection against MES induced convulsions is indicative of possible activity as an anticonvulsant for the prevention of grand mal **epileptic seizures**; see Epilepsia 10:315 (1969).
SUMM . . . react with the active compounds. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, vegetable **oils**, polyethylene glycols, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume **oil**, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized. . .
DETD . . . containing 7 ml of 1 N HCl. The organic layer was then dried (MgSO.sub.4), filtered and concentrated. The resulting orange **oil** was chromatographed on silica gel. Elution with hexane-ether (98:2) afforded 0.38 g (31%) of recovered diphenyl disulfide, mp 60.degree., mmp. . .
DETD . . . the R.sub.f values, the broad leading spot and slowest moving spot were identified as iodobenzene and methaqualone, respectively. The yellow **oil** was chromatographed on silica gel. After the residual iodobenzene had been washed off the column with hexane, elution with hexane-ether (9:1) afforded ca. 15 mg of a clear nonviscous **oil**: .sup.1 H NMR (CDCl.sub.3) 8.28 (d, J=8, 1H, 5-H), 7.73-6.83 (m, 17H, aromatic), 5.08 (s, 1H, CH) and 2.93 ppm. . .
DETD . . . ether. The ethereal extracts were combined, dried (MgSO.sub.4) and concentrated at room temperature. TLC analysis (hexane-ether-acetone, 70:25:5) of the yellow **oil** revealed a three-component mixture. The major component, the title compound, was located between the two minor components corresponding to the. . .
DETD Trituration of the **oil** with hexane afforded 0.91 g (51%) of crude product which was a yellow solid, mp 119.degree.-128.degree.Further purification by recrystallization of. . .
DETD A 2.50 g (52 mmol) sample of 50% sodium hydride-mineral **oil** dispersion was washed with 30 ml of hexane and filtered, and the **oil**-free sodium hydride was quickly added to the reaction flask along with 150 ml of dry DME. The resulting gray slurry. . .
DETD . . . chloride and excess absolute ethanol) for a reaction period of 3.5 hours and using workup Method A afforded a brown **oil** which solidified on standing. The crude product was recrystallized from isopropanol-chloroform-hexane to yield 3.3 g (81%). An analytical sample was. . .
DETD . . . g (11 mmol) of ethyl cinnamate for a period of 2.5 hours,

followed by workup Method A, afforded a brown **oil** which on trituration with hexane-ether gave a yellow solid that was recrystallized from isopropanol-ether to yield 0.64 g (19%) of. . .

DETD To a stirred gray slurry of 1.26 g (30 mmol) of sodium hydride, as a 57%

mineral **oil** dispersion in 100 ml of dry THF, was added a solution of 1.30 g (5 mmol) of ethyl p-trifluoroacetamidobenzoate in. . .

DETD To a stirred gray slurry of 1.26 g (30 mmol) of sodium hydride, as a 57%

mineral **oil** dispersion in 100 ml of dry THF, was added a solution of 1.04 g (5 mmol) of ethyl p-acetamidobenzoate in. . .

DETD 1.20 g (25 mmol) of sodium hydride, as a 50% mineral **oil** dispersion, 0.87 g (5 mmol) of 2,3 dimethyl-4(3H)-quinazolinone and 0.75

g (5.5 mmol) of methyl benzoate were used. After a. . .

DETD In this preparation, 2.6 g (54 mmols) of sodium hydride as a 50% mineral

oil dispersion, 1.81 g (12 mmol) of ethyl nicotinate and 1.74 g (10 mmol) of 2,3 dimethyl-4-(3H)-quinazolinone were employed. After a. . .

DETD . . . tissue. Selective action in the test is believed to indicate potential efficacy against absence (petit mal) seizures. The benzodiazepines, e.g. **diazepam**, are the most potent drugs known to act selectively in preventing Metrazol-induced threshold seizures.

DETD (7) that IVd has a higher MES protective index than Ethotoin, Mephenytoin, Phenobarbital, Metharbital, Trimethadione, Paramethadione, Methsuximide, Phensuximide, **Diazepam** and Clonazepam.

L16 ANSWER 30 OF 31 USPATFULL

AB Tri-n-propylacetamide and tri-n-propylacetic acid salts are useful in the treatment of pathological variations of mood and as anticonvulsants and tranquillizers.

AN 76:58499 USPATFULL

TI Tri-N-propylacetic acid derivatives for therapeutic use

IN Pigerol, Charles, St. Ouen, France
Eymard, Pierre Luc, Fontaine, France

PA Labaz, Paris, France (non-U.S. corporation)

PI US 3988472 19761026 <--

AI US 1975-630132 19751110 (5)

RLI ~~Continuation of Ser. No. US 1973-426730, filed on 13 Dec 1973, now~~ abandoned

PRAI FR 1972-43946 19721211

DT Utility

FS Granted

EXNAM Primary Examiner: Friedman, Stanley J.

LREP Mason, Kolehmainen, Rathburn & Wyss

CLMN Number of Claims: 3

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 604

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 3988472 19761026 <--

SUMM . . . invention, when given preventively by intraperitoneal route, are capable at certain doses of protecting some of the animals against the **epileptic seizure** produced by an adequate and predetermined dose of pentylenetetrazol which would be 100% fatal in the

absence of the compound.. . .

SUMM . . . an activity index figure, the rota rod test described above was

also performed using for comparison two known myorelaxants, namely **diazepam** and mephenesin.

SUMM

	Tri-n-propyl-acetamide	**Diazepam**	Mephenesin
NTD.sub.50 in the rota rod test in mg/kg	68	3	100
ED.sub.50 in the traction test in mg/kg	45	2.75	250
Activity index: NTD.sub.50 / ED.sub.50	1.5	1.1	0.4

DETD . . . the sodium sulphate was centrifuged out. The ether was then eliminated by means of a rotatory evaporator which provided an **oil** which crystallized into fine needles which were left under vacuum until a constant weight was obtained. By this means, 113. . .

L16 ANSWER 31 OF 31 USPATFULL

AB Pentanol derivatives of the general formula: ##EQU1## wherein R represents a straight-chain lower alkyl group containing from 1 to 4 carbon atoms and R.sub.1 represents a hydrogen atom or the group CONH.sub.2. They are useful as antidepressant and tranquillizing agents.

AN 75:71759 USPATFULL

TI Pentanol derivatives

IN Benoit-Guyod, Martine Pierrette, Grenoble, France
Benoit-Guyod, Jean-Louis Alain, Grenoble, France
Boucherle, Andre Louis, Corenc-Montfleury, France
Eymard, Pierre Luc, Fontaine, France

PA Labaz, Paris, France (non-U.S. corporation)

PI US 3929869 19751230 <--

AI US 1974-507380 19740919 (5)

RLI Continuation of Ser. No. US 1973-374530, filed on 28 Jun 1973, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Weinberger, Lorraine A.; Assistant Examiner: Killos, Paul J.

LREP Mason, Kolehmainen, Rathburn & Wyss

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 734

PI US 3929869 19751230 <--

SUMM Under these conditions, the LD.sub.50 of the preferred compounds as compared with the LD.sub.50 of a tranquillizer i.e. **diazepam** under the same conditions were found to be as follows:

SUMM

Compound	LD.sub.50 (in mg/kg)
A	1400
B	1370

SUMM These results show that Compounds A and B are much less toxic than **diazepam.**

SUMM For comparison purposes, the same test was carried out with **diazepam** and Compound A using the ED of both compounds and the following results were registered:

SUMM . . . in 1 min.

	Without current	With current
Controls	14.7 .+-. 1.1	2.1 .+-. 0.4
Compound A 20 mg/kg	15.8 .+-. 1.4	5.6 .+-. 1
Diazepam 1 mg/kg	10.6 .+-. 1.3	9 .+-. 1.2

SUMM These figures show that **diazepam** is more active than Compound A. However, the results obtained without current indicate that Compound A is not depressant with respect to the normal motricity of the animals as is **diazepam**. Moreover, **diazepam** has no antidepressant properties.

SUMM The index obtained for Compound A was 70 and that for **diazepam** was 55 which shows that Compound A is more advantageous than **diazepam.**

SUMM . . . invention, when given preventively by intraperitoneal route, were capable at certain doses of protecting some of the animals against the **epileptic seizure** produced by an adequate and predetermined dose of pentylenetetrazol which would be 100% fatal in the absence of the compound.

DETD . . . was slowly poured into 30 ml (5 volumes) of cold concentrated ammonia. The precipitate which formed changed into a supernatant **oil**. After decantation, this **oil** crystallized under vacuum into white crystals which were recrystallized twice from ethanol at 65.degree.C.

FULL ESTIMATED COST 97.78 104.15

=> s l14 and l13
L17 31 L14 AND L13

=> s benzyl alcohol
L18 51553 BENZYL ALCOHOL

=> s l17 and l18
L19 10 L17 AND L18

=> dup rem l19
PROCESSING COMPLETED FOR L19
L20 10 DUP REM L19 (0 DUPLICATES REMOVED)

=> d l21 ab bib kwic
L21 NOT FOUND
The L-number entered has not been defined in this session, or it has been deleted. To see the L-numbers currently defined in this session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> d l20 ab bib kwic

L20 ANSWER 1 OF 10 USPATFULL

AB A method for administering a therapeutically effective amount of a biologically active substance to the circulatory system of a mammal including administering a pharmaceutical composition having a total volume of 1-1000 .mu.l to a nasal mucosal membrane of the mammal, the pharmaceutical composition including the therapeutically effective amount of the biologically active substance dissolved or suspended in a volume of 1-1000 .mu.l of an n-ethylene glycol containing vehicle including at least one n-ethylene glycol represented by the formula:

H(OCH.sub.2 CH.sub.2).sub.p OH

wherein p is from 1 to 8, so that upon administration of the pharmaceutical composition to the nasal mucosal membrane, absorption of the biologically active substance through the mucosal membrane and into the blood stream of the mammal rapidly takes place and thereby allows the biologically active substance to exert its therapeutic effect.

AN 97:112440 USPATFULL

TI Method of administering a biologically active substance

IN Bechgaard, Erik, Hellerup, Denmark
Gizurarson, Sveinbjorn, Keflavik, Iceland
Hjortkj.ae butted.r, Rolf Kuhlman, Humleb.ae butted.r, Denmark

PA Bechgaard International Research and Development A/S, Hellerup, Denmark (non-U.S. corporation)

PI US 5693608 19971202 <--

AI US 1995-395838 19950228 (8)

RLI Continuation of Ser. No. US 1993-151802, filed on 15 Nov 1993, now patented, Pat. No. US 5428006 which is a continuation of Ser. No. US 1993-71604, filed on 4 Jun 1993, now abandoned which is a continuation of Ser. No. US 1992-870893, filed on 20 Apr 1992, now abandoned which is a division of Ser. No. US 1991-696564, filed on 8 May 1991, now abandoned

PRAI DK 1990-1170 19900510
DK 1990-2075 19900830

DT Utility

FS Granted

EXNAM Primary Examiner: Davenport, Avis M.
LREP Evenson, McKeown, Edwards & Lenahan P.L.L.C.
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN 16 Drawing Figure(s); 16 Drawing Page(s)
LN.CNT 1823
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5693608 19971202 <--

SUMM . . . must be biocompatible with mucus and hence have a certain degree of hydrophilicity. However, the vehicle should preferably also posses **lipophilic** properties in order to dissolve a physiologically active amount of certain biologically active substances.

SUMM Lau and Slattery (1989) studied the absorption characteristics of **diazepam** and lorazepam following intranasal administration for the treatment of status epilepticus. In order to solubilize these drugs, a non-ionic surfactant, polyoxyethylated castor **oil**, was selected as the least irritating out of several solvents studied including polyethyleneglycol 400. **Diazepam** absorption was 84 and 72%, respectively, in two adults measured over a period of 60 hours.

However, the peak concentration. . . peak (2.3 hours). The authors conclude that the intranasal route of administration had limited potential for the acute treatment of **epileptic seizures**.

SUMM International Patent Publication No. WO 86/04233 discloses a pharmaceutical composition wherein the drug (e.g. **diazepam**) is dissolved in a mixture of propellant and co-solvent e.g. glycerolphosphatide. This composition requires a pressurized system and at least. . .

SUMM wherein p is an integer of 3-8 or in water or in a vegetable **oil** or in a mixture of water and/or n-ethylene glycol and/or vegetable **oil**.

SUMM . . . anti-emetica having a regulatory effect on the motility of the intestine such as domperidon; Anti-epileptica and anti-spasmolytica such as clonazepam, **diazepam**, nitrazepam, lorazepam etc.; Anti-histaminic and histaminic agents such as diphenhydramin HCl, chloropheniramine maleate, clemastine, histamine, prophenpyridamine maleate, chlorprophenpyridamine maleate, disodium. . . citrate, or .alpha..sub.1 -antitrypsin etc.; Sedatives such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ehtyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam, . . . and synthetic modifications thereof etc.; Tranquillisers such as alprozolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam, . . .

SUMM . . . derivatives and analogues thereof and tranquilizer such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate,

fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,.

.

SUMM . . . invention, the active substance is selected among antiepileptica, spasmolytics and tranquilizers selected from the group of benzodiazepines such as clonazepam, **diazepam**, flunitrazepam, triazolamn, lorazepam, nitrazepam or mixtures thereof.

SUMM . . . in addition to the biologically active substance(s). Such carrier may comprise water and/or n-ethylene glycol and/or propylene glycol and/or vegetable **oil** and/or even powdery carrier of e.g. microspheres.

SUMM . . . minor proportions of one or more compound(s) selected from the group consisting of surfactants, absorption promoters, water absorbing polymers, microspheres, **oils**, emulsions, liposomes, substances that inhibit enzymatic degradation, alcohols, organic solvents, water, hydrophobic agents, pH-controlling agents, preservatives and osmotic pressure controlling. . .

SUMM wherein p is 3 to 8 or in water or in a vegetable **oil** or in a mixture of water and/or n-ethylene glycol and/or vegetable **oil**

.

SUMM wherein p is 3 to 8 or in water or in a vegetable **oil** or in a mixture of water and/or n-ethylene glycol and/or vegetable **oil** for application to a mucosal membrane.

SUMM . . . [9004 76-6]). Glycofurol 75 is a colourless liquid miscible with water, alcohols, such as methanol, ethanol, n-proypanol, glycerol and various **oils** in all proportions and has a b.p. about 155.degree. C. GF is reported to cause irritation when used in compositions. . .

SUMM . . . relevant dose for human subjects in only e.g. 25-300 .mu.l of the vehicle. In aqueous solutions clinically relevant doses of **diazepam** and clonazepam will alternatively have to be dissolved in about 5000 ml and >10 ml, respectively.

SUMM The vehicle system according to the invention may be used in combination with various co-solvents, such as vegetable **oil** such as Miglyol.RTM. 840 (Dynamit Nobel Chemie, Troisdorf, W-Germany) or optionally hydrogenated or ethoxylated castor **oil**, which surprisingly increases the possibilities for designing a controlled release--formulation such as a **diazepam** formulation which avoids peak plasma concentrations.

SUMM . . . according to the invention may comprise one or more additional pharmaceutical exipients, such as: surfactants and absorption promoters having a hydrophillic-**lipophilic** balance from about 6 to 26 and ionic as well as non-ionic surfactants including polyoxyethylene alcohol ethers, bile salts and. . . aprotinin; Alcohols, such as, ethanol, glycerol, or benzylalcohol; Organic solvents, such as, ethylacetate, or benzylalcohol; Hydrophobic agents, such as vegetabile **oil**, e.g. soybean **oil**, peanut **oil**, coconut **oil**, corn **oil**, olive **oil**, sunflower **oil**, castor **oil**, Miglyol.RTM. 810/812/840 or mixtures thereof; pH-controlling agents, such as, nitric acid, phosphoric acid, or acetic acid, citrate: Preservatives and osmotic. . .

DRWD FIG. 6 shows a graphical representation showing the mean plasma level of **diazepam** after administration of preparations comprising glyycofuryol and various co-solvents,

DETD . . . .mu.l F in PEG

22 f
23
24
25 m
26
27 5 30 .mu.l F in PEG + GF
1
28 f
29
30

Abbreviations:
D = **Diazepam** 3%; L = Lorazepam 5%; F = Flunitrazepam 1%; PEG = Polyethylene glycol 200; GF = Glycofurol 75; PEG +. . .

DETD 3 mg **diazepam** in 100 .mu.l vehicle was prepared and applied to rabbits in a manner analogous to that described in example 6. The following vehicles were used: (1) Glycofurolum 75 (GF); (2) Miglyol 840+GF (7+3) and (3) Vegetable **oil**+GF (7+3). Blood samples were obtained from the marginal ear vein at following time intervals: 0,

5, 10, 15, 30 and 60 minutes and the **diazepam** concentration was determined by HPLC.

DETD FIG. 6 shows the mean plasma **diazepam** concentrations obtained after the intranasal administration. An initial peak plasma concentration can be controlled dependent on the GF/**oil** vehicle used. The plasma concentration for the GF formulation at 5 minutes is about 55% of an intravenous injection of 3 mg **diazepam** as Stesolid.RTM. (Dumex A/S, Denmark).

DETD . . . added acetic acid 0.4% (pH about 6); (12) as (11) added nitric acid to pH 2. (13) as (11) added **benzyl alcohol** 3%; (14) as (10) added ethanol 16% and **benzyl alcohol** 3%; (15) 4EGf+5% GF adjusted to pH 3.5 with nitric acid (less than 0.01%); (16) as (15) added sodium nitrate. . . (17) as (15) added ethanol 5%; (18) 4EGf+5% GF adjusted to pH 4.2 citric acid (0.1%); (19) as (15) added **benzyl alcohol** 2%; (20) 4EGf+5% GF added sodium nitrate 0.04%.

DETD As seen in table 7, only nitric acid, nitrate, ethanol and **benzyl alcohol** increases the stability. The content of water in 4EGf, GF and PG was about 0.05%. Amazingly the stability in e.g.. . .

DETD Surprisingly it has been found that the intranasal absorption of e.g. benzodiazepines, such as clonazepam and **diazepam**, in the vehicles according to the invention is very similar to an intravenous injection (i.v.). From FIG. 1 it appears. . .

DETD . . . volume is desirable in order to reduce or eliminate a local irritating effect. Alternatively a non irritating co-solvent, e.g. vegetabile **oil**, may be added. In this way a desired dose volume or delivery rate may also be obtained. To reduce plasma. . .

DETD TABLE 2

THE INFLUENCE OF GLYCOFUROLE (% GF) IN TETRAETHYLENEGLYCOL (4EG) AND VEGETABILE **OIL** (OV) IN GF ON THE TIME TO RESPONSE (minutes) AFTER INTRANASAL APPLICATION OF 0.25 mg CLONAZEPAM TO RABBITS (n = 4).

NOTICE:. . .

DETD Lau, S. W. J. and Slattery, J. T. (1989), "Absorption of **diazepam** and lorazepam following intranasal administration." Inernational Journal of Pharmaceutics, 54, 171-174.

CLM What is claimed is:

19. The method according to claim 1 wherein the vehicle further comprises a vegetable **oil**.

IT 50-56-6, Oxytocin, biological studies 50-57-7, Lypressin 146-22-5, Nitrazepam **439-14-5**, Diazepam 846-49-1, Lorazepam 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 9001-25-6, Blood coagulation factor VII 9001-27-8, Blood coagulation factor VIII 9001-28-9, Blood coagulation factor IX 9002-67-9, LH 9002-68-0, FSH 9002-72-6, Growth hormone 9004-10-8, Insulin, biological studies 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9034-40-6, LHRH 11000-17-2, Vasopressin 16679-58-6, DDAVP 28911-01-5, Triazolam 50647-00-2, LTH 58822-25-6, Leucine enkephalin 63631-40-3, DADLE 66960-34-7, Metkephamid
(pharmaceutical intranasal formulation contg.)

=> s l19 and subcutaneous or injection
L21 1579682 L19 AND SUBCUTANEOUS OR INJECTION

=> s subcutaneous or injection
L22 1754152 SUBCUTANEOUS OR INJECTION

=> s l19 and l22
L23 10 L19 AND L22

=> d l23 2-10 ab bib kwic

L23 ANSWER 2 OF 10 USPATFULL
AB The subject compounds, which are adapted for the site-specific/sustained
delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D-DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of
a dihydropyridine .revreaction. pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is lower alkyl or benzyl and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH functional group to the carbonyl function of [DHC], then [D] must be other than a sympathetic-stimulant, steroid sex hormone or long chain alkanol; and

(b) non-toxic pharmaceutically acceptable salts of compounds of formula (I). The corresponding ionic pyridinium salt type drug/carrier entities [D-QC].sup.+ X.sup.- are also disclosed.
AN 96:51023 USPATFULL
TI Brain-specific drug delivery
IN Bodor, Nicholas S., Gainesville, FL, United States
PA University of Florida, Gainesville, FL, United States (U.S. corporation)
PI US 5525727 19960611 <--
AI US 1992-967979 19921028 (7)
RLI Division of Ser. No. US 1991-639283, filed on 10 Jan 1991, now patented,
Pat. No. US 5187158 which is a division of Ser. No. US 1989-295938, filed on 11 Jan 1989, now patented, Pat. No. US 5008257 which is a

division of Ser. No. US 1984-665940, filed on 29 Oct 1984, now patented,
Pat. No. US 4824850 which is a continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 Ser. No. Ser. No. US 1983-461543, filed on 27 Jan 1983, now abandoned Ser. No. Ser. No. US 1983-475493, filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And Ser. No. US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564

PRAI WO 1983-US725 19830519

DT Utility

FS Granted

EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Mach, D. Margaret M.

LREP Burns, Doane, Swecker & Mathis

CLMN Number of Claims: 29

ECL Exemplary Claim: 1

DRWN 8 Drawing Figure(s); 8 Drawing Page(s)

LN.CNT 6632

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5525727 19960611 <--

SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules such as water and urea may pass through the. . . carrier-mediated and active transport processes govern the movement of many molecules through the BBB. Thus, it As generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine-propyl. . .

SUMM . . . in regulating drug concentrations in the CNS. There are several efflux processes: bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.

DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.

DETD . . . dopamine precursor used, for example, in the treatment of Parkinsonism); muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam and phenothiazine tranquilizers such as carphenazine,

fluphenazine and the like; mild and strong analgesics and narcotics; sedatives and. . .

DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)-adenine; 6-azauridine; idoxuridine; trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers, such as **diazepam**, oxazepam, lorazepam, chlordiazepoxide, flurazepam, bromazepam, cnlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers/anticonvulsants such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . or pivalylated. According to Scheme 3 which follows, one specific delivery system for dopamine, compound 5, on administration (e.g., by **injection**) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enters the CNS. Following oxidation both in the brain and in the other. . . quaternary percursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic** derivatization of the catechol system in dopamine has also now been demonstrated.

DETD . . . of 5c. FIG. 6 summarizes such results, and is consistent with the mechanism shown in Scheme 3. After one single **injection** of the 1,4-dihydropyridine derivative 5c to the rat, the dihydroxy quaternary 6a (ion), which is the only detectable derivative, could. . .

DETD . . . appearance of 6a in the brain following administration of 5c. The "trapping" of 6a in the brain subsequent to I.V. **injection** of 5c provides a constant source of a potent dopaminergic agent, either dopamine or 6a itself. The significantly lower effect. . .

DETD Accordingly, provided hereby is a potent, brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protective group(s)], which penetrates. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g., the enkephalins, which have been found to initiate **epileptic seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . system and/or route of administration capable of slowly releasing the chemical, e.g. sustained release tablets and capsules for oral administration; **subcutaneous injection**, or implantation of drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular **injection** of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionite (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph

7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . iodide, 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield,0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very slowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD Male Sprague-Dawley rats of average weight of 150 .+-.10 g were used. The rats were anesthetized with IM **injection** of Inovar and the jugular was exposed. Compound 5c was injected intrajugularly in the form of 10% solution in DMSO at a dose of 64.2 mg/kg (equivalent to 50 mg/kg compound 6a). The **injection** was given at a rate of 24 .mu.l/min using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . decapitated at 15, 30, 60 and 120 min later to collect blood samples. Control rats (time 0) received an I.V. **injection** of the saline vehicle and were decapitated 30 min later. Compound 5c was dissolved in 10% ethanol in saline and. . .

DETD Female Sprague-Dawley rats of average weight of 225.+-.10 g were used. The rats were anaesthetized with IM **injection** of Innovar.RTM. (0.13 ml/kg) and the external jugular was exposed. Compound 43 was injected intrajugularly in the form of 2.5%. . . solution in DMSO at a dose of 40 mg/kg (equivalent to 52.3 mg quaternary 42 or 28.2 mg testosterone). The **injection** was given at a rate of 44.4 .mu.l/minute using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . brain delivery and blood concentration profile of the quaternary derivative and testosterone released, against time, was determined following a single **injection** of the dihydropyridine derivative 43 to female rats. These results were compared to blood and brain kinetics of testosterone following. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

. .

DETD . . . hr, after which time the precipitate was removed by filtration. Solvents were removed at reduced pressure to give an orange **oil** which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta. [(CD.sub.3).sub.2 CO] 9.7. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta. (CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4 .multidot.1/2H.sub.2 O: C, 63.16; H,. . .

DETD . . . the solution was warmed to room temperature. After 24 hours, the solvent was removed under reduced pressure. The resulting dark **oil** was triturated with petroleum ether but no solidification

occurred. Identity of the product was confirmed by NMR analysis. The product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil** . Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to give an orange **oil** . UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 : C, 64.52; H, 6.45; N,. . .

DETD . . . ether was added and then removed (10.times.5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD GABA (4 g, 38.8 mmol) was suspended in 50 ml (0.48 mol) of **benzyl alcohol**. The reaction mixture was stirred, with cooling on an ice bath, while 20 ml SOCl.sub.2 was added dropwise over a. . .

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4. Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1485## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow **oil** which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl aerate left a yellow **oil** which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;. .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1487##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to a gentle reflux and refluxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow **oil** reduced methanolic silver nitrate immediately. The structure

of the product was confirmed by NMR analysis to be: ##STR1489##

DETD . . . and the solution was stirred for 4 hours. The organic layer was dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1490##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidine-dione (2 g, 0.0071 tool) was dissolved in bromoacetyl-chloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. C. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yellow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . a build-up of the concentration of the intermediate charged species (quaternary form) in the brain even after one single bolus **injection** of the starting **lipophilic** chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L23 ANSWER 3 OF 10 USPATFULL

AB This invention provides a rectally administered composition for inhibiting **epileptic seizure** and to its methods of use. The composition contains, in a suitable solvent, an anti-epileptic agent for inhibiting **epileptic seizure**, a buffer for maintaining pH, and a thickener for imparting a viscosity to the composition effective for rectal administration by **injection** to a patient in **epileptic seizure**.

AN 95:96826 USPATFULL

TI Rectally-administered, **epileptic-seizure**-inhibiting composition

IN Evenstad, Kenneth L., Wayzata, MN, United States
O'Neill, Victoria A., Wayzata, MN, United States
Gorham, Thomas R., Brooklyn Park, MN, United States

PA Athena Neurosciences, Inc., San Francisco, CA, United States (U.S. corporation)

PI US 5462740 19951031 <--

AI US 1993-122685 19930917 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Azpuru, Carlos A.

LREP Merchant, Gould, Smith, Edell, Welter & Schmidt

CLMN Number of Claims: 8

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 691

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Rectally-administered, **epileptic-seizure**-inhibiting composition

PI US 5462740 19951031 <--

AB This invention provides a rectally administered composition for inhibiting **epileptic seizure** and to its methods of use. The composition contains, in a suitable solvent, an anti-epileptic agent for inhibiting **epileptic seizure**, a buffer for maintaining pH, and a thickener for imparting a viscosity to the composition effective for rectal administration by **injection** to a patient in **epileptic seizure**.

SUMM This invention relates to rectally administered compositions for inhibiting **epileptic seizure** and to their methods of preparation and application.

SUMM . . . dysrhythmia characterized by an abnormal and excessive EEG (electroencephalograph) discharge and by a disturbance of consciousness.

During an episode of **epileptic seizure**, there may be involuntary body movement or hyperactivity of the autonomic nervous system. Different kinds of **epileptic seizures** can display various clinical phenomena and EEG activities. Such variations in clinical phenomena and EEG activities form the basis of. . .

SUMM Generally, it is desirable to prevent **epileptic seizures** in humans by maintaining effective drug therapy. However, if seizure takes place, particularly for seizures with extensive tonic-clonic duration, such. . . the patient, such as bruises, cuts, broken arms or even damage caused by anoxia. Anti-epileptic drugs (i.e., drugs that inhibit **epileptic seizure**, either before or after the onset of **epileptic seizure**) can be given intravenously for acute inhibition of the **epileptic seizure**. See "Drugs for Epilepsy", The Medical Letter, Vol. 31, Issue 783, 1-4, 1989. However, in situations in

which there is involuntarily convulsive movement, intravenous administration of drugs is not desirable because the patient's uncontrolled movement may hinder **injection** or even cause injuries. Moreover, intravenous **injection** of **diazepam**, a preferred anti-epileptic drug, is sometimes painful and can cause thrombophlebitis, an inflammation of a vein associated with thrombus formation.. . .

SUMM . . . as anti-epileptic agents. See Remington's Pharmaceutical Sciences, supra. A convenient way to administer an anti-epileptic drug such as benzodiazepine, e.g. **diazepam**, is by ingestion so that the drug can be absorbed by the gastro-intestinal tract. Sheth et al. (U.S. Pat. No. 4,126,672) describe a sustained-release capsule for oral administration of **diazepam**. The capsules contain medicaments in combination with a hydrocolloid. Upon contact with gastric fluid, the

hydrocolloid hydrates, forming an outside. . .

SUMM . . . of administering such compositions. The compositions are described as capable of being administered orally, as well as parenterally, i.e. via **subcutaneous**, intramuscular and intravenous **injection**. Fish et al. also disclose that the anti-convulsive compositions may be administered in the form of a rectal

suppository. The. . . anti-convulsive agent into a shapable base material. Suitable suppository bases are described to include cocoa butter, glycerinated gelatin, hydrogenated vegetable **oils**, mixtures of polyethylene glucose, and fatty acid esters of polyethylene glycol.

SUMM However, for a patient having jerking movement because of seizure, the above-mentioned routes of drug administration are not practical. Intravenous **injection** of anti-epileptic agents is difficult.

Oral administration is also impractical if the patient has no voluntary control of skeletal muscles.. . . suppositories are slow-acting and therefore not effective for rendering fast relief of seizure.

Therefore, there is a need for an **epileptic-seizure**-inhibiting composition that can be administered and absorbed quickly and safely.

SUMM The present invention provides a viscous, aqueous-based, **epileptic-seizure**-inhibiting composition effective to inhibit **epileptic seizure**. The composition is suitable for rectal administration by **injection** with a syringe-like applicator. The present invention is also directed to syringe assemblies and cartridges containing the composition and methods of using the assemblies and cartridges for delivery of the present composition. The **epileptic-seizure**-inhibiting composition is preferably a thickened solution that contains these ingredients: solvent, an anti-epileptic agent for inhibiting **epileptic seizure**, a pH adjusting agent such as a buffer system for maintaining a pH suitable for rectal administration, and a thickener for imparting a viscosity to the composition effective for rectal administration by **injection** to a patient in or threatened by **epileptic seizure**.

DETD One embodiment of the present invention is a composition for inhibiting **epileptic seizures** in a patient, such as status epilepticus seizures, acute cluster epilepsy seizures, acute repitctue seizures and febrile seizures. The composition. . . retained inside the patient's rectum without substantial leakage or drainage therefrom. The composition is useful for inhibiting or moderating an **epileptic seizure** in a patient during seizure. However, it can also be used to prevent the onset of seizure.

DETD A wide variety of anti-epileptic agents are known in the art. Many may be utilized in the **epileptic-seizure**-inhibiting composition of this invention. Representative examples of effective anti-epileptic agents include ethynyl amines such as deprenyl, eldeprine and eidepryl barbiturates such as mephobarbital, febarbamate, primidone, and phenobarbital sodium, benzodiazepines such as carbamezepine, lorazepam, and **diazepam**, hydantoins such as phenytoin sodium, mephenytoin and ethotoin BP, oxazolidinediones such as paramethadione and trimethadione, succinimides such as phensuximide and. . .

DETD When a patient is in **epileptic seizure**, in order to ~~minimize injury to the patient due to tonic spasm and clonic movement~~, prompt administration of medication is. . . many anti-epileptic agents, such as phenobarbital, can be used in the invention, the drug of choice is a benzodiazepine, particularly **diazepam**. Because of their relaxing effect in skeletal muscles, benzodiazepines, particularly **diazepam**, are also useful in the present invention for treating various types of epilepsies involving skeletal muscle contraction or spasm.

DETD . . . more anti-epileptic agents in the composition of the present invention. When two or more anti-epileptic agents are present in an **epileptic-seizure**-inhibiting composition, it is important to ensure that there is no deleterious interaction between the anti-epileptic agents so as not to. . .

DETD . . . 0.1-2.5 wt-% of the total composition, preferably about 0.25-1.5 wt-% to about 7.5 wt-%. In the preferred embodiment in which

diazepam is the only anti-epileptic agent in the composition, the concentration of **diazepam** is typically about 0.25-0.75 wt-% of the composition.

DETD Preferably, a dose of **epileptic-seizure**-inhibiting composition is selected so that the effective amount of the anti-epileptic agent is in a suitable volume for a particular. . . a composition of the present invention contains an amount of an anti-epileptic agent which is therapeutically effective to inhibit an **epileptic seizure**. This amount will depend on the particular anti-epileptic agent used. For commercially available anti-epileptic agents, information on the therapeutically effective amount for inhibiting **epileptic seizure** is available to the public.

DETD Typically, the present composition can be administered so that single doses of **diazepam** of about 7.5 mg to 20 mg are delivered to an adult, so as to achieve a dose in the. . . mg/kg. The amount can vary depending on the size and physical condition of the individual. The volume of the present **epileptic-seizure**-inhibiting composition to be administered also will vary with different patients. As a general guideline for using the composition of the present invention, e.g., wherein 0.5 wt-% **diazepam** is the anti-epileptic agent, typically the dosage is about 1.5 ml to about 5 ml for an adult (>12 years),. . .

DETD The **epileptic-seizure**-inhibiting composition of the present invention contains an amount of a thickener effective for rendering the consistency of the composition effective for rectal administration to a patient in **epileptic seizure** by **injection**. To be effective as an injectable, rectally administered **epileptic-seizure**-inhibiting composition, the present composition preferably has a viscosity such that it can be quickly administered by **injection**, yet once administered, does not tend to leak out of or drain from the anus. If the viscosity of the. . . the composition is too high, there may be difficulty in administering the composition into the rectum of a patient by **injection**.

DETD . . . thickeners is used to provide a viscosity within the desired range. The amount of a particular thickener used in the **epileptic-seizure**-inhibiting composition is dependent on the particular thickener used. Typically, the concentration of a suitable thickener such as a cellulose ether. . . .

DETD . . . . is about 7.0. The optimal pH for stability for some anti-epileptic agents is slightly lower than 7. For example, for **diazepam** stability, the optimal pH is about 5.5. It is preferred that the pH of the present composition be adjusted to. . . is acceptable for rectal administration and stability of the anti-epileptic agent. Therefore, typically, the pH of the present composition containing **diazepam** will be neutral or mildly acidic, e.g., about 5.5 to 7.5. Preferably, the pH is about 6.2 to 7.2.

DETD . . . often an anti-epileptic agent supplied in solution form contains suitable pH adjusting agents. One can vary the pH of the **epileptic-seizure**-inhibiting composition by fine-tuning the amount of the pH adjusting agents. For the preferred embodiment with **diazepam** as the anti-epileptic agent, the concentration of benzoic acid can be about 0.01 to 10 wt-% of the composition and. . .

DETD . . . the precipitation thereof. Depending on the particular

anti-epileptic agent, different organic solvents may be used. In the preferred case, wherein **diazepam** is the anti-epileptic agent, 1-2 nontoxic polyols or alkanols such as, propylene glycol and/or ethyl alcohol may be used as. . .

DETD . . . rectum, an organic solvent that can act as a physiologically-acceptable liquid surfactant can be selected to be included in the **epileptic-seizure**-inhibiting composition. An effective surfactant can modify the surface tension of the composition of the invention and facilitate coating of the. . .

DETD . . . solvent or solvents are used in amounts effective to solubilize the anti-epileptic agent and to inhibit precipitation thereof in the **epileptic-seizure**-inhibiting composition, e.g., about 25 to 75 wt-% of a polyol or polyol-alkanol mixture may be employed. In the preferred embodiment in which the **epileptic-seizure**-inhibiting composition contains **diazepam** as the anti-epileptic agent, typically, propylene glycol is present at a concentration of about 25 wt-% to about 60 wt-%. . .

DETD A physiologically-acceptable preservative can be optionally included in the **epileptic-seizure**-inhibiting composition to extend the shelf-life of the composition against bacterial attack. **Benzyl alcohol** is the preferred preservative, although other preservatives, for example, thimerosal, chlorobutanol, methyl parabens, propyl parabens and benzalkonium chloride may also. . . concentration of the preservative needed in a composition varies with the preservative selected. Typically, a preservative is present in the **epileptic-seizure**-inhibiting composition at a concentration of about 0.01 wt-% to about 2.5 wt-% of the composition. For **benzyl alcohol**, the preferred concentration is about 1 wt-% to about 2.0 wt-%.

DETD F. Preparation of the **Epileptic-seizure**-inhibiting Composition

DETD G. Administration of the **Epileptic-seizure** -inhibiting Composition

DETD The **epileptic-seizure**-inhibiting composition is preferably applied to the rectum by an applicator. Typically, the applicator is similar to a syringe. A preferred. . . seizure. The applicator further has a pressuring means associated with or operatively connected to the syringe barrel for forcing the **epileptic-seizure**-inhibiting composition out of the syringe barrel, through the elongated hollow member and into the rectum. For example, the pressuring means. . .

DETD . . . the applicator is made of a material that does not absorb or chemically react with the anti-epileptic agents in the **epileptic -seizure**-inhibiting composition. This is particularly important if the composition is stored in the applicator for an extended period of time. For. . . constructed of a plastic material and another part with glass or metal. For example, a glass cartridge filled with a **diazepam**-containing composition can be inserted into an applicator having a plastic barrel. Because the glass cartridge is surrounded by the plastic. . .

DETD . . . tip member of the applicator in the rectum of the patient, and apply pressure to the barrel to deliver the **epileptic-seizure**-inhibiting composition into the rectum of the patient. It is also preferred to package a specific, premeasured amount of the composition. . .

DETD . . . first end 41 of a cylindrical barrel 40. A generally cylindrical cartridge 50 containing internally a premeasured volume of

an **epileptic-seizure**-inhibiting composition (not shown) and a plunger 60 effective for forcing the composition out of the cartridge 50 can be inserted. . .

DETD The cartridge 50 that can contain the **epileptic-seizure**-inhibiting composition has a hollow cylindrical body portion 55 connected on one end to a hollow neck portion 57 and connected. . .

DETD The applicator 10, including the body 20, the cartridge 50 containing the **epileptic-seizure**-inhibiting composition, and the plunger 60, can be packaged as a unit. The neck portion 57 of the cartridge has an. . . 40. The elongated, hollow member 30 of the applicator 10 is then inserted into the rectum of the patient. The **epileptic-seizure**-inhibiting composition is then administered to the patient by the operator manually engaging the finger grips 70 and the flange 66. . .

DETD Other embodiments of applicator may have flexible bulb-shaped bodies in which the **epileptic-seizure**-inhibiting composition of the present invention is stored. In use, the composition can be forced out of the bulb-shaped body into. . .

DETD While orally and intravenously administered **epileptic-seizure**-inhibiting compositions are not conveniently given to a patient in seizure with tonic spasm and clonic movement, the composition of the present invention is advantageously so employed. The composition of this invention is effective to inhibit **epileptic seizure** because it can be administered into the rectum in seconds and the anti-epileptic agent in the composition is absorbed quickly. . .

DETD The **epileptic-seizure**-inhibiting composition has a viscosity that is low enough that it can be inserted in seconds by using, for example, a. . . absorbed may be unreasonably long for the purpose of inhibiting seizure that is in progress. Clinical studies has shown that **diazepam** suppositories are inappropriate where a rapid effect is required (see Hughes et al., Aust J. Hosp. Pharm., 14:2, 73-75 (1984)).. . .

DETD In intravenously administration of **epileptic-seizure**-inhibiting compositions, the pH of the **epileptic-seizure**-inhibiting composition is maintained at a range that is compatible with the intravenous route of administration. The pH for an intravenously. . . be suitable because there is a less risk of adversely affecting the pH of the blood. As a result, the **epileptic-seizure**-inhibiting composition can have a longer shelf life than intravenous solutions.

DETD **Epileptic-seizure**-inhibiting Composition

DETD Propylene glycol USP (10.6 kg), ethyl alcohol (2.65 kg), and **benzyl alcohol** (0.398 kg) were added to a clean stainless steel mixing vessel and mixed at 730 rpm at 25.degree. C., and. . . benzoic acid USP (0.305 kg) was added into the mixture through a 20 mesh screen and mixed for ten minutes. **Diazepam**, USP (0.128 kg), was added into the mixture and mixed for an additional 20 minutes. Hydroxypropylmethyl cellulose, METHOCEL.TM. E50 LVP. . .

DETD **Epileptic-seizure**-inhibiting Composition

DETD An **epileptic-seizure**-inhibiting composition is made using a procedure analogous to that of Example 1 except 1.0 kg of phenobarbital sodium, USP (Windthrop) is used instead of 0.128 kg of **diazepam**.

DETD **Epileptic-seizure**-inhibiting Composition

DETD An **epileptic-seizure**-inhibiting composition is made using a procedure analogous to that of Example 1 except 0.128 kg of phenytoin sodium, USP (Park-Davis) is used instead of 0.128 kg of **diazepam**.

DETD A comparative, randomized single-dose 2-way crossover bioavailability with the **diazepam** viscous solution of Example 1 and Roche **diazepam** (valium.RTM.) injectable solution was conducted using as subjects 18 healthy adult males, age 18-45 years. A dosage of 15 mg of the composition of Example 1 was administered rectally and Roche valium.RTM. was administered intravenously by **injection**.

DETD . . . present rectal solution was 90.4% relative to the Roche injectable solution. Half-lives were similar and the maximum serum concentrations of **diazepam** (447 ng/ml for the present composition and 584 ng/ml for the Roche injectable) were both above the effective therapeutic concentration. . .

DETD Use of the **Epileptic-seizure**-inhibiting Composition

DETD When a adult patient is observed to have an **epileptic seizure** attack, the kit of Example 1 is opened and the applicator assembled by opening the sealed end of the cartridge. . .

CLM What is claimed is:

1. A viscous, **epileptic-seizure**-inhibiting composition comprising: (a) about 0.1-2.5 wt-% of the total composition of an anti-epileptic agent; (b) a buffer system in an. . . a cellulose ether thickener to impart a viscosity to the composition so that it is suitable for administration by rectal **injection** to a human patient; and (d) about 25-95 wt-% solvent.

3. The composition of claim 2 wherein the anti-epileptic agent is **diazepam**.

8. A viscous, **epileptic-seizure**-inhibiting composition comprising: (a) about 0.25-0.75 wt-% **diazepam**; (b) a buffer system in an amount effective to maintain the pH of the composition at about 5.5-7.5; (c) about. . .

IT **439-14-5**, Diazepam
(rectal antiepileptic compns.)

L23 ANSWER 4 OF 10 USPATFULL

AB A method for administering a therapeutically effective amount of a biologically active substance to the circulatory system of a mammal including administering a pharmaceutical composition having a total volume of 1-1000 .mu.l to a nasal mucosal membrane of the mammal, the pharmaceutical composition including the therapeutically effective amount of the biologically active substance dissolved or suspended in a volume of 1-1000 .mu.l of a n-glycofurol-containing vehicle including at least one n-glycofurol represented by the formula: ##STR1## wherein n is from 1 to 8, so that upon administration of the pharmaceutical composition to the nasal mucosal membrane, absorption of the biologically active substance through the mucosal membrane and into the blood stream of the mammal rapidly takes place and thereby allows the biologically active substance to exert its therapeutic effect.

AN 95:58110 USPATFULL

TI Method of administering a biologically active substance

IN Bechgaard, Erik, Hellerup, Denmark
Gizurarson, Sveinbjorn, Keflavik, Iceland
Hjortkjaer, Rolf K., Humlebaer, Denmark

PA Bechgaard International Research and Development A/S, Hellerup, Denmark (non-U.S. corporation)
PI US 5428006 19950627 <--
AI US 1993-151802 19931115 (8)
DCD 20120314
RLI Continuation of Ser. No. US 1993-71604, filed on 4 Jun 1993, now abandoned which is a continuation of Ser. No. US 1992-870893, filed on 20 Apr 1992, now abandoned which is a division of Ser. No. US 1991-696564, filed on 8 May 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Warden, Jill; Assistant Examiner: Davenport, A. M.
LREP Evenson, McKeown, Edwards & Lenahan
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 12 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 1468
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5428006 19950627 <--
SUMM The administration by **injection** (intravenous, intramuscular and **subcutaneous**) of biologically active substances is normally regarded as the most convenient way of administration when the purpose is to achieve. . . substance is not absorbed or is inactivated in the gastrointestinal tract or by first-pass hepatic metabolism. However, the administration by **injection** presents a range of disadvantages. Thus it requires the use of sterile syringes and may cause pains and irritations, particularly in the case of repeated **injections**, including the risk of infection. Besides, **injections** cannot be administered by untrained persons.
SUMM . . . organism in connection with parenteral administration. Furthermore, this route of administration may conveniently be used as an alternative to parenteral **injection**, when a rapid onset of effect is needed, and it can be performed by an untrained person.
SUMM In order to be an attractive alternative to **injection**, intranasal administration should offer a similar relation of dosis to plasma concentration and should not cause any considerable pain or. . .
SUMM . . . be biocompatible with the mucus and hence have a certain degree of hydrophilicity. However, the vehicle should preferably also posses **lipophilic** properties in order to dissolve a physiologically active amount of certain biologically active substances.
SUMM Lau and Slattery (1989) studied the absorption characteristics of **diazepam** and lorazepam following intranasal administration for the treatment of status epilepticus. In order to solubilize these drugs, a non-ionic surfactant, polyoxyethylated castor **oil**, was selected as the least irritating out of several solvents studied including polyethyleneglycol 400. **Diazepam** absorption was 84 and 72%, respectively, in two adults measured over a period of 60 hours. However, the peak concentration. . . peak (2.3 hours). The authors conclude that the intranasal route of administration had limited potential for the acute treatment of **epileptic seizures**.
SUMM International Patent Publication No. WO 86/04233 discloses a pharmaceutical composition wherein the drug (e.g. **diazepam**) is dissolved in a mixture of propellant and co-solvent e.g. glycerolphosphatide. This composition requires a pressurized system and

at least. . .

SUMM . . . anti-emetica having a regulatory effect on the motility of the intestine such as domperidom; Anti-epileptica and anti-spasmolytica such as clonazepam, **diazepam**, nitrazepam, lorazepam etc.; Anti-histaminic and histaminic agents such as diphenhydramin HCl, chloropheniramine maleate, clemastine, histamine, prophenpyridamine maleate, chlorprophenpyridamine maleate, disodium. . . citrate or .alpha..sub.1 -antitrypsin etc.; Sedatives such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, lorazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. . . and synthetic modifications thereof etc.; Tranquillisers such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. . .

SUMM . . . derivatives and analogues thereof; and tranquilizer such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. .

SUMM . . . invention, the active substance is selected among antiepileptica, spasmolytics and tranquillisers selected from the group of benzodiazepines such as clonazepam, **diazepam**, flunitrazepam, triazolam, lorazepam, nitrazepam or mixtures thereof.

SUMM . . . preparation additionally comprises one or more compound(s) selected from the group consisting of surfactants, absorption promoters, water absorbing polymers, microspheres, **oils**, emulsions, liposomes, substances that inhibit enzymatic degradation, alcohols, organic solvents, water, hydrophobic agents, pH-controlling agents, preservatives and osmotic pressure controlling. . .

SUMM . . . [9004 76-6]). Glycofurol 75 is a colourless liquid miscible with water, alcohols, such as methanol, ethanol, n-propanol, glycerol and various **oils** in all proportions and has a b.p. about 155.degree. C. GF is reported to cause irritation when used in compositions. . .

SUMM A special advantage in using the above vehicle system is that e.g. highly **lipophilic** substances such as the benzodiazepines as well as water soluble substances e.g. peptides and proteins such as the pancreatic hormones. . . relevant dose for human subjects in only e.g. 25-300 .mu.l of the vehicle. In aqueous solutions clinically relevant doses of **diazepam** and clonazepam will alternatively have to be dissolved in about 5000 ml and >10 ml, respectively.

SUMM The vehicle system according to the invention may be used in combination with various co-solvents, such as vegetable **oil** such as Miglyol.RTM. 840 (Dynamit Nobel Chemie, Troisdorf, W-Germany) or optionally hydrogenated or ethoxylated castor **oil**, which

surprisingly increases the possibilities for designing a controlled release-formulation such as a **diazepam** formulation which avoids peak plasma concentrations.

SUMM . . . according to the invention may comprise one or more additional pharmaceutical exipients, such as: surfactants and absorption promoters having a hydrophillic-**lipophilic** balance from about 6 to 26 and ionic as well as non-ionic surfactants including polyoxyethylene alcohol ethers, bile salts and. . . aprotinin; Alcohols, such as, ethanol, glycerol, or benzylalcohol; Organic solvents, such as, ethylacetate, or benzylalcohol; Hydrophobic agents, such as vegetabile **oil**, e.g. soybean **oil**, peanut **oil**, coconut **oil**, corn **oil**, olive **oil**, sunflower **oil**, castor **oil**, Miglyol.RTM. 810/812/840 or mixtures thereof; pH-controlling agents, such as, nitric acid, phosphoric acid, or acetic acid, citrate; Preservatives and osmotic. . .

DRWD FIG. 6 shows a graphical representation showing the mean plasma level of **diazepam** after administration of preparations comprising glycofurol and various co-solvents,

DETD . . . vehicle the local as well as the systemic effect after absorption should be considered. GF is used as excipient in **injection** formulations, where the administered amount is greater than 300 .mu.l per dose, which exceeds the amount administered intranasally using the. . .

DETD . . . 4 30 .mu.l F in PEG
1

20
21
22 f
23
24
25 m 5 30 .mu.l F in PEG + GF
1
26
27
28 f
29
30

Abbreviations:
D = **Diazepam** 3%; L = Lorazepam 5%;
F = Flunitrazepam 1%; PEG = Polyethylene glycol 200;
GF = Glycofurol 75; PEG + GF =. . .

DETD . . . 1 shows the mean plasma clonazepam concentration obtained after the administration. The figure also shows the plasma concentration after i.v. **injection** into the marginal ear vein of the same dose (0.5 mg) of clonazepam as Rivotril.RTM., injected over 1/2 minute. The. . . plasma concentration after intranasal application is about the same or even higher, at about 2 minutes, than for an i.v. **injection**.

DETD . . . pH to 4.0 with 0.1N sodium hydroxide and finally 5% glycofurolum 75 was added. The rabbits were made hypoglycaemic by **subcutaneous injection** of 83 .mu.g insulin one hour prior to the experiment. Blood samples were continuously withdrawn from the marginal ear vein. . .

DETD 3 mg **diazepam** in 100 .mu.l vehicle was prepared and applied to rabbits in a manner analogous to that described in example 6. The following vehicles were used: (1) Glycofurolum 75 (GF); (2) Miglyol

840+GF (7+3) and (3) Vegetable **oil**+GF (7+3). Blood samples were obtained from the marginal ear vein at following time intervals: 0,

5, 10, 15, 30 and 60 minutes and the **diazepam** concentration was determined by HPLC.

DETD FIG. 6 shows the mean plasma **diazepam** concentrations obtained after the intranasal administration. An initial peak plasma concentration can be controlled dependent on the GF/**oil** vehicle used. The plasma concentration for the GF formulation at 5 minutes is about 55% of an intravenous **injection** of 3 mg **diazepam** as Stesolid.RTM. (Dumex A/S, Denmark).

DETD . . . added acetic acid 0.4% (pH about 6); (12) as (11) added nitric acid to pH 2. (13) as (11) added **benzyl alcohol** 3%; (14) as (10) added ethanol 16% and **benzyl alcohol** 3%; (15) 4EGf+5%GF adjusted to pH 3.5 with nitric acid (less than 0.01%); (16) as (15) added sodium nitrate 0.04%: (17) as (15) added ethanol 5%; (18) 4EGf+5%GF adjusted to pH 4.2 citric acid (0.1%); (19) as (15) added **benzyl alcohol** 2%; (20) 4EGf+5%GF added sodium nitrate 0.04%.

DETD As seen in table 7, only nitric acid, nitrate, ethanol and **benzyl alcohol** increases the stability. The content of water in 4EGf, GF and PG was about 0.05%. Amazingly the stability in e.g.. . .

DETD Surprisingly it has been found that the intranasal absorption of e.g. benzodiazepines, such as clonazepam and **diazepam**, in the vehicles according to the invention is very similar to an intravenous **injection** (i.v.). From FIG. 1 it appears that the peak clonazepam plasma concentration (t.sub.max) is reached within less than 2-3 minutes. . .

DETD . . . E2, was studied in pilot. Two formulations containing 30% and 100% glycofurol (GF), respectively, were tested i.n. relative to an i.v.-**injection** of the same dose.

DETD The formulations for i.v.-**injection** and for intranasal application were prepared just before the administration. Formulation 1 for i.v. administration was prepared by dissolving 2.729. . .

DETD . . . the mean .+-. S.D. estrogen (E2) plasma concentrations after administration of about 50 .mu.g estrogen to rabbits (n=3) as an i.v.-**injection** (formulation 1) or intranasal administration (2 i.n. and 3 i.n. formulated with glycofurol (GF) 100% and 30%, respectively).

DETD . . . shows the mean .+-.S.D. estrone (E1) plasma concentrations after administration of about 50 .mu.g estrogen to rabbits (n=3) as an i.v.-**injection** (formulation 1) or intranasal administration (2 i.n. and 3 i.n. formulated with glycofurol (GF) 100% and 30%, respectively).

DETD TABLE 10

Individual estrogen (E2) plasma concentrations after administration of about 50 .mu.g estrogen to rabbits (n = 3) as an i.v.-**injection** (formulation 1) or intranasal administration (2 i.n. and 3 i.n. formulated with glycofurol (GF) 100% and 30%, respectively).

	E2 plasma concentration								Dose/
Formula-									
Rabbit. . .									

DETD TABLE 11

Individual estrogen (E1) plasma concentrations after administration of about 50 .mu.g estrogen

to rabbits (n = 3) as an i.v.-**injection**
(formulation 1) or intranasal administration (2 i.n.
and 3 i.n. formulated with glycofurol (GF)
100% and 30%, respectively).
E2 plasma concentration
Dose/
Formula-
Rabbit. . .
DETD . . . mean i.v. dose) for estrogen (E2) and
estrone (E1) after single administration of
about 50 .mu.g estrogen (n = 3) as an i.v.-**injection**
(1 i.v.) or intranasal administration (2 i.n. and 3 i.n.)
Observed mean
% Relative to
(dose corrected)
1 i.v.-mean .+-. SD
Parameter. . .
DETD . . . dose volume is desirable in order to reduce or eliminate local irritating effect. Alternatively a non irritating co-solvent, e.g. vegetabile **oil**, may be added. In this way a desired dose volume or delivery rate may also be obtained. To reduce plasma. . .
DETD Lau, S. W. J. and Slattery, J. T. (1989), "Absorption of **diazepam** and lorazepam following intranasal administration." International Journal of Pharmaceutics, 54,171-174.
CLM What is claimed is:
. . . method according to claim 5 wherein the benzodiazepine is at least one member selected from the group consisting of clonazepam, **diazepam**, flunitrazepam, triazolam, lorazepam, and nitrazepam.

10. A method according to claim 5 wherein the benzodiazepine is **diazepam**.

14. A method according to claim 1 wherein the vehicle further comprises a vegetable **oil**.

IT 50-56-6, Oxytocin, biological studies 50-57-7, Lypressin 146-22-5, Nitrazepam **439-14-5**, Diazepam 846-49-1, Lorazepam 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 9001-25-6, Blood coagulation factor VII 9001-27-8, Blood coagulation factor VIII 9001-28-9, Blood coagulation factor IX 9002-67-9, LH 9002-68-0, FSH 9002-72-6, Growth hormone 9004-10-8, Insulin, biological studies 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9034-40-6, LHRH 11000-17-2, Vasopressin 16679-58-6, DDAVP 28911-01-5, Triazolam 50647-00-2, LTH 58822-25-6, Leucine enkephalin 63631-40-3, DADLE 66960-34-7, Metkephamid
(pharmaceutical intranasal formulation contg.)

L23 ANSWER 5 OF 10 USPATFULL
AB A pharmaceutical preparation for application of an effective amount of one or more biologically active substance(s) to a mucosal membrane of a mammal comprising an n-glycofurol represented by the formula I:
##STR1##
wherein n is 1 to 4 in an amount from: 0.1-30% preferably 0.1-20% most preferably 1-15% in water, or in vegetable **oil** or n-ethylene glycol(s) represented by formula II:

H(OCH.sub.2 CH.sub.2).sub.p OH

wherein p is 2 to 8, or in a mixture thereof. Nasal administration of the preparation produces a high plasma concentration of the

pharmaceutically active substance(s) nearly as rapid as by i.v. administration.

AN 95:22893 USPATFULL

TI Pharmaceutical preparation

IN Bechgaard, Erik, Hellerup, Denmark
Gizurarson, Sveinbjorn, Keflavik, Iceland
Hjortkjaer, Rolf K., Humlebaer, Denmark

PA Bechgaard International Research and Development A/S, Hellerup, Denmark (non-U.S. corporation)

PI US 5397771 19950314 <--

AI US 1993-118683 19930910 (8)

RLI Continuation of Ser. No. US 1991-791651, filed on 14 Nov 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-696564, filed on 8 May 1991, now abandoned

PRAI DK 1990-1170 19900510
DK 1990-2075 19900830

DT Utility

FS Granted

EXNAM Primary Examiner: Lee, Lester L.; Assistant Examiner: Davenport, A. M.

LREP Wegner, Cantor, Mueller & Player

CLMN Number of Claims: 29

ECL Exemplary Claim: 1

DRWN 16 Drawing Figure(s); 16 Drawing Page(s)

LN.CNT 1854

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5397771 19950314 <--

AB . . . n is 1 to 4 in an amount from: 0.1-30% preferably 0.1-20% most preferably 1-15% in water, or in vegetable **oil** or n-ethylene glycol(s) represented by formula II:

SUMM The administration by **injection** (intravenous, intramuscular and **subcutaneous**) of biologically active substances is normally regarded as the most convenient way of administration when the purpose is to achieve. . . substance is not absorbed or is inactivated in the gastrointestinal tract or by first-pass hepatic metabolism. However, the administration by **injection** presents a range of disadvantages. Thus it requires the use of sterile syringes and may cause pains and irritations, particularly in the case of repeated **injections**, including the risk of infection. Besides, **injections** cannot be administered by untrained persons.

SUMM . . . organism in connection with parenteral administration. Furthermore, this route of administration may conveniently be used as an alternative to parenteral **injection**, when a rapid onset of effect is needed, and it can be performed by an untrained person.

SUMM In order to be an attractive alternative to **injection**, intranasal administration should offer a similar relation of dosis to plasma concentration and should not cause any considerable pain or. . .

SUMM . . . be biocompatible with the mucus and hence have a certain degree of hydrophilicity. However, the vehicle should preferably also posses **lipophilic** properties in order to dissolve a physiologically active amount of certain biologically active substances.

SUMM Lau and Slattery (1989) studied the absorption characteristics of **diazepam** and lorazepam following intranasal administration for the treatment of status epilepticus. In order to solubilize these drugs, a non-ionic surfactant. polyoxyethylated castor **oil**, was selected as the least irritating out of several solvents studied including polyethyleneglycol 400. **Diazepam** absorption was 84

and 72%, respectively, in two adults measured over a period of 60 hours.

However, the peak concentration. . . peak (2.3 hours). The authors conclude that the intranasal route of administration had limited potential for the acute treatment of **epileptic seizures**.

SUMM International Patent Publication No. WO 86/04233 discloses a pharmaceutical composition wherein the drug (e.g. **diazepam**) is dissolved in a mixture of propellant and co-solvent e.g. glycerolphosphatide. This composition requires a pressurized system and at least. . .

SUMM wherein p is an integer of 3-8 or in water or in a vegetable **oil** or in a mixture of water and/or n-ethylene glycol and/or vegetable **oil**.

SUMM . . . anti-emetica having a regulatory effect on the motility of the intestine such as domperidon; Anti-epileptica and anti-spasmolytica such as clonazepam, **diazepam**, nitrazepam, lorazepam etc.; Anti-histaminic agents and histaminic agents such as diphenhydramin HCl, chloropheniramine maleate, clemastine, histamine, prophenpyridamine maleate, chlorprophenpyridamine maleate,. . . citrate, or .alpha..sub.1 -antitrypsin etc.; Sedatives such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. . . and synthetic modifications thereof etc.; Tranquillisers such as alprazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. . .

SUMM . . . derivatives and analoguss thereof; and tranquilizer such as alpazolam, bromazepam, brotizolam, camazepam, chlordiazepeoxide, clobazam, chlorazepic acid, clonazepam, clotiazepam, cloxazolam, delorazepam, **diazepam**, estazolam, ethyl loflazepate, fludiazepam, flunitrazepam, flurazepam, flutazolam, halazepam, haloxazolam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordiazepam, oxazepam, oxazolam,. .

SUMM . . . invention, the active substance is selected among antiepileptica, spasmolytics and tranquilizers selected from the group of benzodiazepines such as clonazepam, **diazepam**, flunitrazepam, triazolamn, lorazepam, nitrazepam or mixtures thereof.

SUMM . . . in addition to the biologically active substance(s). Such carrier may comprise water and/or n-ethylene glycol and/or propylene glycol and/or vegetable **oil** and/or even powdery carrier of e.g. microspheres.

SUMM . . . minor proportions of one or more compound(s) selected from the group consisting of surfactants, absorption promoters, water absorbing polymers, microspheres, **oils**, emulsions, liposomes, substances that inhibit enzymatic degradation, alcohols, organic solvents, water, hydrophobic agents, pH-controlling agents, preservatives and osmotic pressure controlling. . .

SUMM wherein p is 3 to 8 or in water or in a vegetable **oil** or in a mixture of water and/or n-ethylene glycol and/or vegetable **oil** .

SUMM wherein p is 3 to 8 or in water or in a vegetable **oil** or in a mixture of water and/or n-ethylene glycol and/or vegetable **oil** for application to a mucosal membrane.

SUMM . . . [9004 76-6]). Glycofurol 75 is a colourless liquid miscible with water, alcohols, such as methanol, ethanol, n-propanol, glycerol and various **oils** in all proportions and has a b.p. about 155.degree. C. GF is reported to cause irritation when used in compositions. . .

SUMM A special advantage in using the above vehicle system is that e.g. highly **lipophilic** substances such as the benzodiazepines as well as water soluble substances e.g. peptides and proteins such as the pancreatic hormones. . . relevant dose for human subjects in only e.g. 25-300 .mu.l of the vehicle. In aqueous solutions clinically relevant doses of **diazepam** and clonazepam will alternatively have to be dissolved in about 5000 ml and >10 ml, respectively.

SUMM The vehicle system according to the invention may be used in combination with various co-solvents, such as vegetable **oil** such as Miglyol.RTM. 840 (Dynamit Nobel Chemie, Troisdorf, W-Germany) or optionally hydrogenated or ethoxylated castor **oil**, which surprisingly increases the possibilities for designing a controlled release--formulation such as a **diazepam** formulation which avoids peak plasma concentrations.

SUMM . . . according to the invention may comprise one or more additional pharmaceutical exipients, such as: surfactants and absorption promoters having a hydrophillic-**lipophilic** balance from about 6 to 26 and ionic as well as non-ionic surfactants including polyoxyethylene alcohol ethers, bile salts and. . . aprotinin; Alcohols, such as, ethanol, glycerol, or benzylalcohol; Organic solvents, such as, ethylacetate, or benzylalcohol; Hydrophobic agents, such as vegetabile **oil**, e.g. soybean **oil**, peanut **oil**, coconut **oil**, corn **oil**, olive **oil**, sunflower **oil**, castor **oil**, Miglyol.RTM. 810/812/840 or mixtures thereof; pH-controlling agents, such as, nitric acid, phosphoric acid, or acetic acid, citrate; Preservatives and osmotic. . .

DRWD FIG. 6 shows a graphical representation showing the mean plasma level of **diazepam** after administration of preparations comprising glycofurol and various solvents,

DETD . . . as well as the systemic effect after absorption should be considered. GF and PEG 400 is used as excipient in **injection** formulations, where the administered amount is greater than 300 .mu.l per dose, which exceeds the amount administered intranasally using the. . .

DETD . . . .mu.l F in PEG 1

20
21
22 f
23
24
25 m 5 30 .mu.l F in PEG + GF 1
26
27
28 f
29

Abbreviations:
D = **Diazepam** 3%; L = Lorazepam 5%; F = Flunitrazepam 1%; PEG = Polyethylene glycol 200; GF = Glycofurol 75; PEG +. . .

DETD . . . I shows the mean plasma clonazepam concentration obtained after the administration. The figure also shows the plasma concentration after i.v. **injection** into the marginal ear vein of the same dose (0.5 mg) of clonazepam as Rivotril.RTM., injected over 1/2 minute. The. . . plasma concentration after intranasal application is about the same or even higher, at about 2 minutes, than for an i.v. **injection**.

DETD . . . pH to 4.0 with 0.1N sodium hydroxide and finally 5% glycofurolum 75 was added. The rabbits were made hypoglycaemic by **subcutaneous injection** of 83 .mu.g insulin one hour prior to the experiment. Blood samples were continuously withdrawn from the marginal ear vein. . .

DETD 3 mg **diazepam** in 100 .mu.l vehicle was prepared and applied to rabbits in a manner analogous to that described in example 6. The following vehicles were used: (1) Glycofurolum 75 (GF); (2) Miglyol 840+GF (7+3) and (3) Vegetable **oil**+GF (7+3). Blood samples were obtained from the marginal ear vein at following time intervals: 0, 5, 10, 15, 30 and 60 minutes and the **diazepam** concentration was determined by HPLC.

DETD FIG. 6 shows the mean plasma **diazepam** concentrations obtained after the intranasal administration. An initial peak plasma concentration can be controlled dependent on the GF/**oil** vehicle used. The plasma concentration for the GF formulation at 5 minutes is about 55% of an intravenous **injection** of 3 mg **diazepam** as Stesolid.RTM. (Dumex A/S, Denmark).

DETD . . . added acetic acid 0.4% (pH about 6); (12) as (11) added nitric acid to pH 2. (13) as (11) added **benzyl alcohol** 3%; (14) as (10) added ethanol 16% and **benzyl alcohol** 3%; (15) 4EGf+5%GF adjusted to pH 3.5 with nitric acid (less than 0.01%); .(16) as (15) added sodium nitrate 0.04%; f17) as (15) added ethanol 5%; (18) 4EGf+5%GF adjusted to pH 4.2 citric acid (0.1%); (19) as (15) added **benzyl alcohol** 2%; (20) 4EGf+5%GF added sodium nitrate 0.04 %.

DETD As seen in table 7, only nitric acid, nitrate, ethanol and **benzyl alcohol** increases the stability. The content of water in 4EGf, GF and PG was about 0.05%. Amazingly the stability in e.g.. . .

DETD Surprisingly it has been found that the intranasal absorption of e.g. benzodiazepines, such as clonazepam and **diazepam**, in the vehicles according to the invention is very similar to an intravenous **injection** (i.v.). From FIG. 1 it appears that the peak clonazepam plasma concentration (t.sub.max) is reached within less than 2-3 minutes. . .

DETD . . . E2, was studied in pilot. Two formulations containing 30% and 100% glycofurol (GF), respectively, were tested i.n. relative to an i.v.-**injection** of the same dose.

DETD The formulations for i.v.-**injection** and for intranasal application were prepared just before the administration. Formulation 1 for i.v. administration was prepared by dissolving 2.729. . .

DETD . . . shows the mean .+-.S.D. estrogen (E2) plasma concentrations after administration of about 50 .mu.g estrogen to rabbits (n=3) as an i.v.-**injection** (formulation 1) or intranasal administration (2

i.n. and 3 i.n. formulated with glycofurol (GF) 100% and 30%, respectively).

DETD . . . shows the mean .+-.S.D. estrone (E1) plasma concentrations after administration of about 50 .mu.g estrogen to rabbits (n=3) as an i.v.-**injection** (formulation 1) or intranasal administration (2 i.n. and 3 i.n. formulated with glycofurol (GF) 100% and 30%, respectively).

DETD TABLE 10

Individual estrogen (E2) plasma concentration after administration of about 50 .mu.g estrogen to rabbits (n = 3) as an i.v.-**injection** (formulation 1) or intranasal administration (2 i.n. and 3 i.n. formulated with glycofurol (GF) 100% and 30%, respectively).
n.d. = lower than 0.04. . .

DETD TABLE 11

Individual estrogen (E1) plasma concentration after administration of about 50 .mu.g estrogen to rabbits (n = 3) as an i.v.-**injection** (formulation 1) or intranasal administration (2 i.n. and 3 i.n. formulated with glycofurol (GF) 100% and 30%, respectively).
n.d. = lower than 0.04. . .

DETD . . . mean i.v. dose)
for estrogen (E2) and estrone (E1) after single administration of about 50 .mu.g estrogen (n = 3) as an i.v.-**injection** (1 i.v.) or intranasal administration (2 i.n. and 3 i.n.).
AUC (nmol ml.sup.+1 min) is the area under the plasma concentration - time. . .

DETD . . . volume is desirable in order to reduce or eliminate a local irritating effect. Alternatively a non irritating co-solvent, e.g. vegetabile **oil**, may be added. In this way a desired dose volume or delivery rate may also be obtained. To reduce plasma. . .

DETD Table 5 indicates that; intranasal application (of e.g. 10% GF) may act just as quickly as intravenous **injection** (in 2.8 min (i.n.) and 4.2 min (i.v.), respectively) in spite of the fact that the plasma level is higher. . .

DETD TABLE 2

THE INFLUENCE OF GLYCOFUROLE (% GF) IN TETRAETHYLENEGLYCOL (4EG) AND VEGETABLE **OIL** (OV)
IN GF ON THE TIME TO RESPONSE (minutes) AFTER INTRANASAL APPLICATION OF 0.25 mg CLONAZEPAM TO
RABBITS (n = 4).
NOTICE: THE TIME. . .

DETD

Vehicle no.:	Dose (mg):	Formulation:
1	0.50	Rivotril .RTM. IV-**injection**
2	0.50	10% GF in 4EG
3	0.25	10% GF in 4EG
4	0.25	Pure GF
5	0.25	70% GF in 4EG
6	0.25	Pure. . .

DETD

Vehicle no.:	Dose (mg):	Formulation:
1	0.50	Rivotril .RTM. IV-**injection**
2	0.50	10% GF in 4EG
3	0.25	10% GF in 4EG

4 0.25 Pure GF
5 0.25 70% GF in 4EG
6 0.25 Pure. . .
DETD
Vehicle no.: Dose (mg): Formulation:

1 0.50 Rivotril .RTM. IV-**injection**
2 0.50 10% GF in 4EG
3 0.25 10% GF in 4EG
4 0.25 Pure GF
5 0.25 70% GF in 4EG
6 0.25 Pure. . .

DETD Lau, S. W. J. and Slattery, J. T. (1989), "Absorption of **diazepam** and lorazepam following intranasal administration." International Journal of Pharmaceutics, 54, 171-174.

CLM What is claimed is:

. . . n is from 1 to 4, the vehicle further comprising a component selected from the group consisting of water, vegetable **oil**, n-ethylene glycol(s) represented by the formula II: H(OCH.sub.2 CH.sub.2).sub.p OH wherein p is 3 to 8, and mixtures thereof, so. . .

. . . 13. The method according to claim 12, wherein the biologically active substance is selected from the group consisting of clonazepam, **diazepam**, flunitrazepam, triazolam, lorazepam, nitrazepam and mixtures thereof.

. . . n is from 1 o 4, the vehicle further comprising a component selected from the group consisting of water, vegetable **oil**, n-ethylene glycol(s) represented by the formula II: H(OCH.sub.2 CH.sub.2).sub.p OH wherein p is 3 or 4, and mixtures thereof.

. . . pharmaceutical composition according to claim 22, wherein the biologically active substance is selected from the , group consisting of clonazepam, **diazepam**, flunitrazepam, triazolam, iorazepam, bitrazepam and mixtures thereof.

IT 50-56-6, Oxytocin, biological studies 50-57-7, Lypressin 146-22-5, Nitrazepam **439-14-5**, Diazepam 846-49-1, Lorazepam 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 9001-25-6, Blood coagulation factor VII 9001-27-8, Blood coagulation factor VIII 9001-28-9, Blood coagulation factor IX 9002-67-9, LH 9002-68-0, FSH 9002-72-6, Growth hormone 9004-10-8, Insulin, biological studies 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9034-40-6, LHRH 11000-17-2, Vasopressin 16679-58-6, DDAVP 28911-01-5, Triazolam 50647-00-2, LTH 58822-25-6, Leucine enkephalin 63631-40-3, DADLE 66960-34-7, Metkephamid
(pharmaceutical intranasal formulation contg.)

L23 ANSWER 6 OF 10 USPATFULL

AB The subject compounds, which are adapted for the site-specific/sustained delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D-DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine .revreaction. pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is lower alkyl or benzyl and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH functional group to the carbonyl function of [DHC], then [D] must be other than a sympathetic stimulant, steroid sex hormone or long chain alkanol; and

(b) non-toxic pharmaceutically acceptable salts of compounds of formula (I) wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine .revreaction. pyridinium salt redox carrier. The corresponding ionic pyridinium salt type drug/carrier entities [D-QC].sup.+ X.sup.- are also disclosed.

AN 93:12516 USPATFULL
TI Brain-specific drug delivery
IN Bodor, Nicholas S., Gainesville, FL, United States
PA University of Florida, Gainesville, FL, United States (U.S. corporation)
PI US 5187158 19930216 <--
AI US 1991-639283 19910110 (7)
RLI Division of Ser. No. US 1989-295938, filed on 11 Jan 1989, now patented, Pat. No. US 5008257 which is a division of Ser. No. US 1984-665940, filed on 29 Oct 1984, now patented, Pat. No. US 4824850 which is a continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 And a continuation-in-part of Ser. No. US 1983-461543, filed on 27 Jan 1983, now abandoned And a continuation-in-part of Ser. No. US 1985-733463, filed on 13 May 1985, now patented, Pat. No. US 4727079 And a continuation-in-part of Ser. No. US 1983-475493, filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And a continuation-in-part of Ser. No. US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564
PRAI CA 1983-428192 19830516
DT Utility
FS Granted
EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Turnipseed, James H.
LREP Burns, Doane, Swecker & Mathis
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 6314
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5187158 19930216 <--
SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules

such as water and urea may pass through the. . . carrier-mediated and
active transport processes govern the movement of many molecules through
the BBB. Thus, it is generally accepted that **lipid** solubility,
degree of ionic dissociation or protonation and the ability of temporary
combination with membrane constituents affect delivery through the. .
. their ease to pass into the brain (as reflected by the different
times of onset of anesthetic action) and their **lipid**/water
partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123,
79 (1957). The role of **lipid** solubility in drug penetration
through the BBB is also exemplified by the better absorption of the
sparingly water-soluble thiamine propyl. . .

SUMM . . . in regulating drug concentrations in the CNS. There are several
efflux processes: bulk flow via the arachnoid villi, diffusion of
lipid soluble substances into brain and blood, active transport
and metabolism by adjacent meninges. Once a drug or metabolite enters
the. . . mechanism associated with the choroid plexus or other
nondefined structures in the CSF compartments. It is generally accepted
that highly **lipid**-soluble drugs leave the CSF more rapidly
than poorly **lipid**-soluble ones, but the barrier to passage of
compounds from CSF has only superficial similarity to the blood-CSF
barrier.

DETD The term "lipoidal" as used herein is intended to designate a carrier
moiety which is **lipid**-soluble or **lipophilic**.

DETD . . . dopamine precursor used, for example, in the treatment of
Parkinsonism); muscle relaxants, tranquilizers and antidepressants,
e.g., benzodiazepine tranquilizers such as **diazepam** and
oxazepam and phenothiazine tranquilizers such as carphenazine,
fluphenazine and the like; mild and strong analgesics and narcotics;
sedatives and. . .

DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside;
(S)-9-(2,3-dihydroxypropyl)-adenine; 6-azaurinde; idoxuridine;
trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-
D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be
mentioned benzodiazepine tranquilizers, such as **diazepam**,
oxazepam, lorazepam, chlordiazepoxide, flurazepam, bromazepam,
chlorazepate, nitrazepam and temazepam; hydantoin-type
tranquilizers/anticonvulsants such as phenytoin, ethotoin, mephenytoin;
phenothiazine-type tranquilizers such as. . .

DETD . . . or pivalylated. According to Scheme 3 which follows, one
specific delivery system for dopamine, compound 5, on administration
(e.g., by **injection**) is distributed throughout the body and by
reason of its **lipophilic** character facilely penetrates the
blood-brain barrier and enter the CNS. Following oxidation both in the
brain and in the other. . . quaternary precursor 6 to the drug
(dopamine) is relatively slow, same permits a sustained release of
dopamine. Too, the simultaneous protection/**lipophilic**
derivatization of the catechol system in dopamine has also now been
demonstrated.

DETD . . . of 5c. FIG. 6 summarizes such results, and is consistent with
the mechanism shown in Scheme 3. After one single **injection** of
the 1,4-dihydropyridine derivative 5c to the rat, the dihydroxy
quaternary 6a (ion), which is the only detectable derivative, could. .
.

DETD . . . appearance of 6a in the brain following administration of 5c.
The "trapping" of 6a in the brain subsequent to I.V. **injection**

of 5c provides a constant source of a potent dopaminergic agent, either dopamine or 6a itself. The significantly lower effect. . .

DETD Accordingly, provided hereby is a potent, brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protective group(s)], which penetrates. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g., the enkephalins, which have been found to initiate **epileptic seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . system and/or route of administration capable of slowly releasing the chemical, e.g. sustained release tablets and capsules for oral administration; **subcutaneous injection**, or implantation of drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular **injection** of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionite (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield, 0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very slowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD Male Sprague-Dawley rats of average weight of 150.+-.10 g were used. The rats were anesthetized with IM **injection** of Inovar and the jugular was exposed. Compound 5c was injected intrajugularly in the form of 10% solution in DMSO at a dose of 64.2 mg/kg (equivalent to 50 mg/kg compound 6a). The **injection** was given at a rate of 24 .mu.l/min using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . decapitated at 15, 30, 60 and 120 min later to collect blood samples. Control rats (time 0) received an I.V. **injection** of the saline vehicle and were decapitated 30 min later. Compound 5c was dissolved in 10% ethanol in saline and. . .

DETD Female Sprague-Dawley rats of average weight of 225.+-.10 g were used. The rats were anaesthetized with IM **injection** of Innovar.RTM. (0.13 ml/kg) and the external jugular was exposed. Compound 43 was injected intrajugularly in the form of 2.5%. . . solution in DMSO at a dose of 40 mg/kg (equivalent to 52.3 mg quaternary 42 or 28.2 mg testosterone). The **injection** was given at a rate of 44.4 .mu.l/minute using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . brain delivery and blood concentration profile of the quaternary derivative and testosterone released, against time, was determined following a single **injection** of the dihydropyridine

derivative 43 to female rats. These results were compared to blood and brain kinetics of testosterone following. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

. .

DETD . . . hr, after which time the precipitate was removed by filtration.

Solvents were removed at reduced pressure to give an orange **oil** which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta.[(CD.sub.3).sub.2 CO] 9.7 (bs,. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta. (CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4 .multidot.1/2H.sub.2 O: C, 63.16; H,. . .

DETD . . . the solution was warmed to room temperature. After 24 hours, the solvent was removed under reduced pressure. The resulting dark **oil** was triturated with petroleum ether but no solidification occurred. Identity of the product was confirmed by NMR analysis. The product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil** . Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to give an orange **oil** . UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 : C, 64.52; H, 6.45; N,. . .

DETD . . . ether was added and then removed (10.times.5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD GABA (4 g, 38.8 mmol) was suspended in 50 ml (0.48 mol) of **benzyl alcohol**. The reaction mixture was stirred, with cooling on an ice bath, while 20 ml SOCl.sub.2 was added dropwise over a. . .

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4.

Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1581## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow **oil** which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl acetate left a yellow

oil which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;.

. .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1583##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to

a gentle reflux and refluxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange

solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow **oil** reduced methanolic silver nitrate immediately. The structure of the product was confirmed by NMR analysis to be: ##STR1585##

DETD . . . and the solution was stirred for 4 hours. The organic layer was

dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1586##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidinedione (2 g, 0.0071 mol) was dissolved in bromoacetylchloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. C. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yellow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . a build-up of the concentration of the intermediate charged species (quaternary form) in the brain even after one single bolus **injection** of the starting **lipophilic** chemical delivery

system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L23 ANSWER 7 OF 10 USPATFULL
AB The subject compounds, which are adapted for the site-specific/sustained
delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D-DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of
a dihydropyridine.revreaction.pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is a lower alkyl or benzyl
and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH functional group to the carbonyl function of [DHC], then [D] must be other than a sympathetic stimulant, steroid sex hormone or long chain alkanol; and

(b) non-toxic pharmaceutically acceptable salts of compounds of formula (I) wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of
a dihydropyridine.revreaction.pyridinium salt redox carrier. The corresponding ionic pyridinium salt type drug/carrier entities [D-QC].sup.+ X.sup.- are also disclosed.
AN 91:30479 USPATFULL
TI Brain-specific drug delivery
IN Bodor, Nicholas S., Gainesville, FL, United States
PA University of Florida, Gainesville, FL, United States (U.S. corporation)
PI US 5008257 19910416 <--
AI US 1989-295938 19890111 (7)
RLI Division of Ser. No. US 1984-665940, filed on 29 Oct 1984, now patented,
Pat. No. US 4824850 which is a continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932
Ser. No. Ser. No. US 1983-461543, filed on 27 Jan 1983, now abandoned
Ser. No. Ser. No. US 1985-733463, filed on 13 May 1985, now patented, Pat. No. US 4622218 Ser. No. Ser. No. US 1983-475493, filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And Ser. No. US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564
PRAI CA 1983-428192 19830516
DT Utility
FS Granted
EXNAM Primary Examiner: Stoll, Robert L.; Assistant Examiner: Covert, John M.
LREP Baumeister, Mary Katherine
CLMN Number of Claims: 28
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 6383
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5008257 19910416 <--
SUMM . . . of theories concerning the nature of the barrier have been

proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules such as water and urea may pass through the. . . carrier-mediated and active transport processes govern the movement of many molecules through the BBB. Thus, it is generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .

SUMM . . . in regulating drug concentrations in the CNS. There are several efflux processes bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.

DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.

DETD . . . dopamine precursor used, for example, in the treatment of Parkinsonism); muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam and phenothiazine tranquilizers such as carphenazine, fluphenazine and the like; mild and strong analgesics and narcotics; sedatives and. . .

DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)adenine; 6-azauridine; idoxuridine; trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers, such as **diazepam**, oxazepam, lorazepam, chlordiazepoxide, flurazepam, bromazepam, chlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers/anti-convulsants such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . or pivalylated. According to Scheme 3 which follows, one specific delivery system for dopamine, compound 5, on administration (e.g., by **injection**) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enters the CNS. Following oxidation both in the brain and in the other. . . quaternary precursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic**

derivatization of the catechol system in dopamine has also now been demonstrated.

DETD . . . of 5c. FIG. 6 summarizes such results, and is consistent with the mechanism shown in Scheme 3. After one single **injection** of the 1,4-dihydropyridine derivative 5c to the rat, the dihydroxy quaternary 6a (ion), which is the only detectable derivative, could. . .

DETD . . . of 6a in the brain following administration of 5c. The "trapping" of b 6a in the brain subsequent to I.V. **injection** of 5c provides a constant source of a potent dopaminergic agent, either dopamine or 6a itself. The significantly lower effect. . .

DETD Accordingly, provided hereby is a potent, brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protective group(s)], which penetrates. . .

DETD 2. **Diazepam**: ##STR44## This reaction scheme utilizes conventional opening of the 7-member ring, accompanied by coupling of the drug to the carrier.. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g., the enkephalins, which have been found to initiate **epileptic seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . system and/or route of administration capable of slowly releasing the chemical, e.g. sustained release tablets and capsules for oral administration; **subcutaneous injection**, or implantation of drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular **injection** of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionite (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . iodide, 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield,0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very slowly U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD Male Sprague-Dawley rats of average weight of 150.+-.10 g were used. The rats were anesthetized with IM **injection** of Inovar and the jugular was exposed. Compound 5c was injected intrajugularly in the form of 10% solution in DMSO at a dose of 64.2 mg/kg (equivalent to 50 mg/kg compound 6a). The **injection** was given at a rate of 24 .mu.l/min using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . decapitated at 15, 30, 60 and 120 min later to collect blood samples. Control rats (time 0) received an I.V. **injection** of the saline vehicle and were decapitated 30 min later. Compound 5c was

dissolved in 10% ethanol in saline and. . .

DETD Female Sprague-Dawley rats of average weight of 225.+-.10 g were used. The rats were anaesthetized with IM **injection** of Innovar.RTM. (0.13 ml/kg) and the external jugular was exposed. Compound 43- was injected intrajugularly in the form of 2.5%. . . . solution in DMSO at a dose of 40 mg/kg (equivalent to 52.3 mg quaternary 42 or 28.2 mg testosterone). The **injection** was given at a rate of 44.4 .mu.l/minute using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . brain delivery and blood concentration profile of the quaternary derivative and testosterone released, against time, was determined following a single **injection** of the dihydropyridine derivative 43 to female rats. These results were compared to blood and brain kinetics of testosterone following. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

. .

DETD . . . hr, after which time the precipitate was removed by filtration.

Solvents were removed at reduced pressure to give an orange **oil** which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta. [(CD.sub.3).sub.2 CO] 9.7. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta. (CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4.

1/2H.sub.2 O: C, 63.16; H,. . .

DETD . . . the solution was warmed to room temperature. After 24 hours, the solvent was removed under reduced pressure. The resulting dark **oil** was triturated with petroleum ether but no solidification occurred. Identity of the product was confirmed by NMR analysis. The product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil**

. Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to give an orange **oil** . UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 : C, 64.52; H, 6.45; N,. . .

DETD . . . ether was added and then removed (10.times.5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD GABA (4 g, 38.8 mmol) was suspended in 50 ml (0.48 mol) of **benzyl alcohol**. The reaction mixture was stirred, with cooling on an ice bath, while 20 ml SOCl.sub.2 was added dropwise over a. . .

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4. Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1506## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow **oil** which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl aetate left a yellow **oil** which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;. . .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1508##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to a gentle reflux and relfuxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow **oil** reduced methanolic silver nitrate immediately. The structure of the product was confirmed by NMR analysis to be: ##STR1510##

DETD . . . and the solution was stirred for 4 hours. The organic layer was dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1511##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidinedione (2 g, 0.0071 mol) was dissolved in bromoacetylchloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. C. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yellow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . a build-up of the concentration of the intermediate charged species (quaternary form) in the brain even after one single bolus **injection** of the starting **lipophilic** chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L23 ANSWER 8 OF 10 USPATFULL

AB The subject compounds, which are adapted for the site-specific/sustained delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D--DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine.revreaction.pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is lower alkyl or benzyl and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH function group to the carbonyl function of [DHC], then [D] must be other than a sympathetic stimulant, steroid sex hormone or long chain alkanol; and

(b) non-toxic pharmaceutically acceptable salts of compounds of formula (I) wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine.revreaction.pyridinium salt redox carrier. The corresponding ionic pyridinium salt type drug/carrier entitles [D==QC].sup.+ X.sup.- are also disclosed.

AN 90:11422 USPATFULL

TI Brain-specific drug delivery of steroid sex hormones cleaved from pyridinium carboxylates and dihydro-pyridine carboxylate precursors

IN Bodor, Nicholas S., Gainesville, FL, United States

PA University of Florida, Gainesville, FL, United States (U.S. corporation)

PI US 4900837 19900213 <--

AI US 1987-76191 19870721 (7)

DCD 20020910

RLI Division of Ser. No. US 1984-665940, filed on 29 Oct 1984, now patented, Pat. No. US 4824850 which is a continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 And a continuation-in-part of Ser. No. US 1983-461543, filed on 27 Jan 1983, now abandoned And a continuation-in-part of Ser. No. US 1983-475493,

filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And a continuation-in-part of Ser. No. US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564

PRAI JP 1982-101940 19820614
CA 1983-428192 19830516
IE 1983-1149 19830517
ZA 1983-3521 19830517
ES 1983-522489 19830517
IT 1983-48327 19830518

DT Utility
FS Granted
EXNAM Primary Examiner: Rotman, Alan R.
LREP Baumeister, Mary Katherine, Clarke, Dennis P.
CLMN Number of Claims: 41
ECL Exemplary Claim: 1,27
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 6389
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4900837 19900213 <--

SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules such as water and urea may pass through the. . . carrier-mediated and active transport processes govern the movement of many molecules through the BBB. Thus, it is generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .

SUMM . . . in regulating drug concentrations in the CNS. There are several efflux processes: bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.

DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.

DETD . . . dopamine precursor used, for example, in the treatment of Parkinsonism); muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam and phenothiazine tranquilizers such as carphenazine, fluphenazine and the like; mild and strong analgesics and narcotics;

sedatives and. . .

DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)adenine; 6-azauridine; idoxuridine; trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers, such as **diazepam**, oxazepam, lorazepam, chloridazepoxide, flurazepam, bromazepam, chlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers/anticonvulsants such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . or pivalylated. According to Scheme 3 which follows, one specific delivery system for dopamine, compound 5, on administratio (e.g., by **injection**) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enters the CNS. Following oxidation both in the brain and in the other. . . quaternary precursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic** derivatization of the catechol system in dopamine has also now been demonstrated.

DETD . . . of 5c. FIG. 6 summarizes such results, and is consistent with the mechanism shown in Scheme 3. After one single **injection** of the 1,4-dihydropyridine derivative 5c to the rat, the dihydroxy quaternary 6a (ion), which is the only detectable derivative, could. . .

DETD . . . appearance of 6a in the brain following administration of 5c. The "trapping" of 6a in the brain subsequent to I.V. **injection** of 5c provides a constant source of a potent dopaminergic agent, either dopamine or 6a itself. The significantly lower effect. . .

DETD Accordingly, provided hereby is a potent, brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protectiv group(s)], which penetrates. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g, the enkephalins, which have been found to initiate **epileptic**, **seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . system and/or route of administration capable of slowly releasing the chemical, e.g. sustained release tablets and capsules for oral administration; **subcutaneous injection**, or implantation of drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular **injection** of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionate (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol)

sodium dithionite. Yield, 0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very sowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD Male Sprague-Dawley rats of average weight of 150.+-.10 g were used. The rats were anesthetized with IM **injection** of Inovar and the jugular was exposed. Compound 5c was injected intrajugularly in the form of 10% solution in DMSO at a dose of 64.2 mg/kg (equivalent to 50 mg/kg compound 6a). The **injection** was given at a rate of 24 .mu.l/min using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . decapitated at 15, 30, 60 and 120 min later to collect blood samples. Control rats (time 0) received an I.V. **injection** of the saline vehicle and were decapitated 30 min later. Compound 5c was dissolved in 10% ethanol in silane and. . .

DETD Female Sprague-Dawley rats of average weight of 225.+-.10 g were used. The rats were anesthetized with IM **injection** of Innovar.sup.R (0.13 ml/kg) and the external jugular was exposed. Compound 43 was injected intrajugularly in the form of 2.5%. . . solution in DMSO at a dose of 40 mg/kg (equivalent to 52.3 mg quaternary 42 or 28.2 mg testosterone). The **injection** was given at a rate of 44.4 .mu.l/minute using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . brain delivery and blood concentration profile of the quaternary derivative and testosterone released, against time, was determined following a single **injection** of the dihydropyridine derivative 43 to female rats. These results were compared to blood and brain kinetics of testosterone following. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

. .

DETD . . . hr, after which time the precipitate was removed by filtration. Solvents were removed at reduced pressure to give an orange **oil** which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta.[(CD.sub.3).sub.2 CO] 9.7 (bs,. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta.(CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine 4-5+C--H);. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4.1/2H.sub.2 O: C, 63.16; H, 5.88;. . .

DETD . . . the solution was warmed to room temperature. After 24 hours, the solvent was removed under reduced pressure. The resulting dark **oil** was triturated with petroleum ether but no solidification occurred. Identity of the product was confirmed by NMR analysis. The

product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil** . Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to given an orange **oil**. UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 O: C, 64.52; H, 6.45; N,. . .

DETD . . . MgSO.sub.4. The ether layer was decanted from the drying agent and the solvent was removed under reduced pressure. To the **oil** residue, ether was added and then removed (10.times.5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD GABA (4 g, 38.8 mmol) was suspended in 50 ml (0.48 mol) of **benzyl alcohol**. The reaction mixture was stirred, with cooling on an ice bath, while 20 ml SOCl.sub.2 was added dropwise over a. . .

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4. Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1569## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow **oil** which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl aetate left a yellow **oil** which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;. .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1571##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to a gentle reflux and refluxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow

oil reduced methanolic silver nitrate immediately. The structure of the product was confirmed by NMR analysis to be: ##STR1573##

DETD . . . and the solution was stirred for 4 hours. The organic layer was

dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1574##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidinedione (2 g, 0.0071 mol) was dissolved in bromoacetylchloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. c. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yelllow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . a build-up of the concentration of the intermediate charged species (quarternary form) in the brain even after one single bolus **injection** of the starting **lipophilic** chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L23 ANSWER 9 OF 10 USPATFULL

AB The subject compounds, which are adapted for the site-specific/sustained
delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D--DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of

a dihydropyridine .revreaction. pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is lower alkyl or benzyl and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH functional group to the carbonyl function of [DHC], then [D] must be other than a sympathetic stimulant, steroid sex hormone or long chain alkanol; and

(b) non-boxic pharmaceutically acceptable salts of compounds of formula (I) wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of

a dihydropyridine .revreaction. pyridinium salt redox carrier. The corresponding ionic pyridinium salt type drug/carrier entities [D--QC].sup.+ X.sup.- are also disclosed.

AN 89:92627 USPATFULL

TI Brain-specific drug delivery
IN Bodor, Nicholas S., Gainesville, FL, United States
PA University of Florida, Gainesville, FL, United States (U.S. corporation)
PI US 4880921 19891114 <--
AI US 1987-75830 19870720 (7)
DCD 20020910
RLI Division of Ser. No. US 1984-665940, filed on 29 Oct 1984, now patented,
Pat. No. US 4824850 which is a continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 And
a continuation-in-part of Ser. No. US 1983-461543, filed on 27 Jan 1983,
now abandoned And a continuation-in-part of Ser. No. US 1983-475493, filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And a continuation-in-part of Ser. No. US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564
PRAI JP 1982-101940 19820614
CA 1983-428192 19830516
IE 1983-1149 19830517
ZA 1983-3521 19830517
ES 1983-522489 19830517
IT 1983-48327 19830518
DT Utility
FS Granted
EXNAM Primary Examiner: Robinson, Douglas W.; Assistant Examiner: Lipovsky, Joseph A.
LREP Baumeister, Mary Katherine, Clarke, Dennis P.
CLMN Number of Claims: 54
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 6386
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4880921 19891114 <--
SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a **fat**-like layer interspersed with small pores, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such
a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules
such as water and urea may pass through the. . . carrier-mediated and
active transport processes govern the movement of many molecules through
the BBB. Thus, it is generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary
combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123, 79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .
SUMM . . . in regulating drug concentrations in the CNS. There are several

efflux processes: bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.

DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.

DETD . . . dopamine precursor used, for example, in the treatment of Parkinsonism); muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam and phenothiazine tranquilizers such as carphenazine, fluphenazine and the like; mild and strong analgesics and narcotics; sedatives and. . .

DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)-adenine; 6-azauridine; idoxuridine; trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers, such as **diazepam**, oxazepam, lorazepam, chlordiazepoxide, flurazepam, bromazepam, chlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers/anticonvulsants such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . or pivalylated. According to Scheme 3 which follows, one specific delivery system for dopamine, compound 5, on administration (e.g., by **injection**) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enters the CNS. Following oxidation both in the brain and in the other. . . quaternary percursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic** derivatization of the catechol system in dopamine has also now been demonstrated.

DETD . . . of 5c. FIG. 6 summarizes such results, and is consistent with the mechanism shown in Scheme 3. After one single **injection** of the 1,4-dihydropyridine derivative 5c to the rat, the dihydroxy quaternary 6a (ion), which is the only detectable derivative, could. . .

DETD . . . appearance of 6a in the brain following administration of 5c. The "trapping" of 6a in the brain subsequent to I.V. **injection** of 5c provides a constant source of a potent dopaminergic agent, either dopamine or 6a itself. The significantly lower effect. . .

DETD Accordingly, provided hereby is a potent brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protective group(s)], which penetrates. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g., the enkephalins, which have been found to initiate **epileptic seizures**, has led to the design of a variety of long lasting potent antagonists.

DETD . . . system and/or route of administration capable of slowly releasing the chemical, e.g. sustained release tablets and capsules for

oral administration; **subcutaneous injection**, or implantation of drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular **injection** of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionite (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield, 0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very slowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD Male Sprague-Dawley rats of average weight of 150.+-.10 g were used. The rats were anesthetized with IM **injection** of Inovar and the jugular was exposed. Compound 5c was injected intrajugularly in the form of 10% solution in DMSO at a dose of 64.2 mg/kg (equivalent to 50 mg/kg compound 6a). The **injection** was given at a rate of 24 .mu.l/min using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . decapitated at 15, 30, 60 and 120 min later to collect blood samples. Control rats (time 0) received an I.V. **injection** of the saline vehicle and were decapitated 30 min later. Compound 5c was dissolved in 10% ethanol in saline and. . .

DETD Female Sprague-Dawley rats of average weight of 225.+-.10 g were used. The rats were anaesthetized with IM **injection** of Innovar.RTM. (0.13 ml/kg) and the external jugular was exposed. Compound 43 was injected intrajugularly in the form of 2.5%. . . solution in DMSO at a dose of 40 mg/kg (equivalent to 52.3 mg quaternary 42 or 28.2 mg testosterone). The **injection** was given at a rate of 44.4 821/minute using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . brain delivery and blood concentration profile of the quaternary derivative and testosterone released, against time, was determined following a single **injection** of the dihydropyridine derivative 43 to female rats. These results were compared to blood and brain kinetics of testosterone following. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

. .

DETD . . . hr, after which time the precipitate was removed by filtration. Solvents were removed at reduced pressure to give an orange **oil** which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil**

(118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta.[(CD.sub.3).sub.2 CO] 9.7 (bs,. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta. (CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4.1/2H.sub.2 O: C, 63.16; H, 5.88;. . .

DETD . . . the solution was warmed to room temperature. After 24 hours, the solvent was removed under reduced pressure. The resulting dark **oil** was triturated with petroleum ether but no solidification occurred. Identity of the product was confirmed by NMR analysis. The product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil** . Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to give an orange **oil** . UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 : C, 64.52; H, 6.45; N,. . .

DETD . . . ether was added and then removed (10.times.5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD GABA (4 g, 38.8 mmol) was suspended in 50 ml (0.48 mol) of **benzyl alcohol**. The reaction mixture was stirred, with cooling on an ice bath, while 20 ml SOCl.sub.2 was added dropwise over a. . .

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4. Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1499## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow **oil** which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl aetate left a yellow **oil** which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to

dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;. . .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1501##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to a gentle reflux and relfuxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow **oil** reduced methanolic silver nitrate immediately. The structure of the product was confirmed by NMR analysis to be: ##STR1503##

DETD . . . and the solution was stirred for 4 hours. The organic layer was dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1504##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidinedione (2 g, 0.0071 mol) was dissolved in bromoacetylchloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. C. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yellow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . a build-up of the concentration of the intermediate charged species (quaternary form) in the brain even after one single bolus **injection** of the ~~starting~~ **lipophilic** chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

L23 ANSWER 10 OF 10 USPATFULL

AB The subject compounds, which are adapted for the site-specific/sustained delivery of centrally acting drug species to the brain, are:

(a) compounds of the formula

[D--DHC] (I)

wherein [D] is a centrally acting drug species, and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of a dihydropyridine.revreaction.pyridinium salt redox carrier, with the proviso that when [DHC] is ##STR1## wherein R is lower alkyl or benzyl

and [D] is a drug species containing a single NH.sub.2 or OH functional group, the single OH group when present being a primary or secondary OH group, said drug species being linked directly through said NH.sub.2 or OH function group to the carbonyl function of [DHC], then [D] must be other than a sympathetic stimulant, steroid sex hormone or long chain alkanol; and

(b) non-toxic pharmaceutically acceptable salts of compounds of formula (I) wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating lipoidal form of

a dihydropyridine.revreaction.pyridinium salt redox carrier. The corresponding ionic pyridinium salt type drug/carrier entitles [D--QC].sup.+ X.sup.- are also disclosed.

AN 89:32284 USPATFULL
TI Brain-specific drug delivery
IN Bodor, Nicholas S., Gainesville, FL, United States
PA University of Florida, Gainesville, FL, United States (U.S. corporation)
PI US 4824850 19890425 <--
AI US 1984-665940 19841029 (6)
RLI Continuation-in-part of Ser. No. US 1982-379316, filed on 18 May 1982, now patented, Pat. No. US 4479932 And a continuation-in-part of Ser. No. US 1983-461543, filed on 27 Jan 1983, now abandoned And a continuation-in-part of Ser. No. US 1983-475493, filed on 15 Mar 1983, now patented, Pat. No. US 4622218 And a continuation-in-part of Ser. No. US 1983-516382, filed on 22 Jul 1983, now patented, Pat. No. US 4540564
PRAI CA 1983-428192 19830516
DT Utility
FS Granted
EXNAM Primary Examiner: Gron, Teddy S.; Assistant Examiner: Thomas, J. E.
LREP Baumeister, Mary Katherine, Clarke, Dennis P.
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 6396
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4824850 19890425 <--

SUMM . . . of theories concerning the nature of the barrier have been proposed. The widely accepted concept describes the boundary as a ~~fat-like layer interspersed with small pores~~, although the BBB is not a simple, anatomically well-defined unitary physical entity. Shuttleworth, Prog. Exp. Tumor Res., 17, 279 (1972). Penetration of such a barrier may occur by several processes: **lipid** soluble substances may passively penetrate into the cells, while small molecules such as water and urea may pass through the. . . carrier-mediated and active transport processes govern the movement of many molecules through the BBB. Thus, it is generally accepted that **lipid** solubility, degree of ionic dissociation or protonation and the ability of temporary combination with membrane constituents affect delivery through the. . . their ease to pass into the brain (as reflected by the different times of onset of anesthetic action) and their **lipid**/water partition coefficient. Mark et al, J. Pharmacol. and Exp. Therap., 123,

79 (1957). The role of **lipid** solubility in drug penetration through the BBB is also exemplified by the better absorption of the sparingly water-soluble thiamine propyl. . .

SUMM . . . in regulating drug concentrations in the CNS. There are several efflux processes: bulk flow via the arachnoid villi, diffusion of **lipid** soluble substances into brain and blood, active transport and metabolism by adjacent meninges. Once a drug or metabolite enters the. . . mechanism associated with the choroid plexus or other nondefined structures in the CSF compartment. It is generally accepted that highly **lipid**-soluble drugs leave the CSF more rapidly than poorly **lipid**-soluble ones, but the barrier to passage of compounds from CSF has only superficial similarity to the blood-CSF barrier.

DETD The term "lipoidal" as used herein is intended to designate a carrier moiety which is **lipid**-soluble or **lipophilic**.

DETD . . . dopamine precursor used, for example, in the treatment of Parkinsonism); muscle relaxants, tranquilizers and antidepressants, e.g., benzodiazepine tranquilizers such as **diazepam** and oxazepam and phenothiazine tranquilizers such as carphenazine, fluphenazine and the like; mild and strong analgesics and narcotics; sedatives and. . .

DETD . . . phenyl-6-chloro-6-deoxy-.beta.-D-glucopyranoside; (S)-9-(2,3-dihydroxypropyl)adenine; 6-azauridine; idoxuridine; trifluridine; BDVU (bisdihydroxyvinyluridine); and 5,6-dichloro-1-.beta.-D-ribofuranosylbenzimidazole. Among the tranquilizers, there can be mentioned benzodiazepine tranquilizers, such as **diazepam**, oxazepam, lorazepam, chloridazepoxide, flurazepam, bromazepam, chlorazepate, nitrazepam and temazepam; hydantoin-type tranquilizers/anticonvulsants such as phenytoin, ethotoin, mephenytoin; phenothiazine-type tranquilizers such as. . .

DETD . . . or pivalylated. According to Scheme 3 which follows, one specific delivery system for dopamine, compound 5, on administratio (e.g., by **injection**) is distributed throughout the body and by reason of its **lipophilic** character facilely penetrates the blood-brain barrier and enters the CNS. Following oxidation both in the brain and in the other. . . quaternary precursor 6 to the drug (dopamine) is relatively slow, same permits a sustained release of dopamine. Too, the simultaneous protection/**lipophilic** derivatization of the catechol system in dopamine has also now been demonstrated.

DETD . . . of 5c. FIG. 6 summarizes such results, and is consistent with the mechanism shown in Scheme 3. After one single **injection** of the 1,4-dihydropyridine derivative 5c to the rat, the dihydroxy quaternary 6a (ion), which is the only detectable derivative, could. . .

DETD . . . appearance of 6a in the brain following administration of 5c. The "trapping" of 6a in the brain subsequent to I.V. **injection** of 5c provides a constant source of a potent dopaminergic agent, either dopamine or 6a itself. The significantly lower effect. . .

DETD Accordingly, provided hereby is a potent, brain-specific dopaminergic agent comprising a **lipophilic** dihydropyridine carrier-type chemical delivery system of dopamine ["pro-prodrug" or "pro-pro-prodrug" in the case of the catechol protectiv group(s)], which penetrates. . .

DETD . . . carrier.fwdarw.quaternary transformation. Also, the brain-specific delivery of small peptides consistent herewith, e.g, the enkephalins, which have been found to initiate **epileptic**,

seizures, has led to the design of a variety of long lasting potent antagonists.

DETD . . . system and/or route of administration capable of slowly releasing the chemical, e.g. sustained release tablets and capsules for oral administration; **subcutaneous injection**, or implantation of drugs in solid pellet form (for example, distributed in a biodegradable polymer); intramuscular **injection** of the compound in solution in **oil** or suspended in a repository vehicle; a transdermal delivery device or form such as an ointment to be applied locally. . .

DETD . . . separated, washed with water, dried with Na.sub.2 SO.sub.4 and distilled under vacuo. Yield 2.3 g (72%) of bright yellow, viscous **oil** was obtained which gave positive test for dihydropyridine with alcoholic silver nitrate solution. U.V. max (buffer pH 7.4) 210 and. . .

DETD . . . dithionate (7.1 g, 0.04 mol) and sodium bicarbonate (5.0 g, 0.06 mol). Yield 1.8 g (76%) of bright yellow, viscous **oil** which reduced alcoholic silver nitrate solution. U.V. max (buffer ph 7.4) 210, 290 and 360 nm; NMR (CDCl.sub.3) .delta. 7.2. . .

DETD . . . 1.0 g (0.012 mol) sodium bicarbonate and 1.42 g (0.008 mol) sodium dithionite. Yield, 0.60 g (84%) of orange-yellow viscous **oil** which reduced alcoholic silver nitrate, but very sowly. U.V. max (buffer pH 7.4) 205 and 390 nm. NMR (CDCl.sub.3) 7.33. . .

DETD Male Sprague-Dawley rats of average weight of 150.+-.10 g were used. The rats were anesthetized with IM **injection** of Inovar and the jugular was exposed. Compound 5c was injected intrajugularly in the form of 10% solution in DMSO at a dose of 64.2 mg/kg (equivalent to 50 mg/kg compound 6a). The **injection** was given at a rate of 24 .mu.l/min using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . decapitated at 15, 30, 60 and 120 min later to collect blood samples. Control rats (time 0) received an I.V. **injection** of the saline vehicle and were decapitated 30 min later. Compound 5c was dissolved in 10% ethanol in silane and. . .

DETD Female Sprague-Dawley rats of average weight of 225.+-.10 g were used. The rats were anesthetized with IM **injection** of Innovar.sup.R (0.13 ml/kg) and the external jugular was exposed. Compound 43 was injected intrajugularly in the form of 2.5%. . . solution in DMSO at a dose of 40 mg/kg (equivalent to 52.3 mg quaternary 42 or 28.2 mg testosterone). ~~The **injection** was given at a rate of~~ 44.4 .mu.l/minute using a calibrated infusion pump. After appropriate time periods, 1 ml of. . .

DETD . . . brain delivery and blood concentration profile of the quaternary derivative and testosterone released, against time, was determined following a single **injection** of the dihydropyridine derivative 43 to female rats. These results were compared to blood and brain kinetics of testosterone following. . .

DETD . . . water, 0.01N HCl and water. The organic layer was dried over Na.sub.2 SO.sub.4 and after evaporation of the solvent an **oil** was obtained. Crystallization from CHCl.sub.3 /petroleum ether yielded 7.4 g (0.014 mol, 76%) m.p. 104.degree.-107.degree. C., of N-.alpha.-t-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycine ethyl ester..

. .

DETD . . . hr, after which time the precipitate was removed by filtration.

Solvents were removed at reduced pressure to give an orange **oil**

which was taken into chloroform (15 ml) and washed with cold water (5 ml). Removal of solvent in vacuo gave. . .

DETD . . . apparent after 6 hours, at which time heat was removed and solvents were evaporated in vacuo to leave a red-orange **oil** (118 mg). The **oil** was dissolved in d.sub.6 acetone and insoluble particles were removed by filtration through a cotton plug. .delta.[(CD.sub.3).sub.2 CO] 9.7 (bs,. . .

DETD . . . layers were dried over sodium sulfate at 0.degree. C. in the dark. Removal of solvent in vacuo gave a yellow-orange **oil** which reduced methanolic AgNO.sub.3 : yield 77 mg, 97%, .delta.(CDCl.sub.3) 6.5-5.9 (bd, 1H, pyridine H-6); 4.5-5.1 (m, 2H, pyridine 4-5+C--H);. . .

DETD . . . the solution was stirred overnight. The precipitated dicyclohexylurea (DCU) was removed by filtration. Additional DCU was removed by triturating the **oil** with hot water. The product was purified with acetone. Calculated for C.sub.17 H.sub.18 N.sub.2 O.sub.4.1/2H.sub.2 O: C, 63.16; H, 5.88;. . .

DETD . . . the solution was warmed to room temperature. After 24 hours, the solvent was removed under reduced pressure. The resulting dark **oil** was triturated with petroleum ether but no solidification occurred. Identity of the product was confirmed by NMR analysis. The product. . .

DETD . . . g, 2.76 ml). The solution was stirred overnight at ambient temperature and the solvent was removed under reduced pressure. The **oil** was stirred overnight with petroleum ether and then dried in vacuo, but no solidification occurred. Identity of the product was. . .

DETD . . . with ethyl ether. The combined organic layers were dried over anhydrous Na.sub.2 SO.sub.4 and reduced in volume. The resultant orange **oil** oxidized ethanolic silver nitrate. Identity of the product was confirmed by NMR analysis.

DETD . . . was added, with stirring. The solution was then stirred overnight. The solvent was removed under reduced pressure and the resulting **oil** was dissolved in aqueous methanol and extracted with ethyl ether. The product was obtained as a pale yellow **oil** . Its identity was confirmed by NMR analysis.

DETD . . . The ether layer was dried over Na.sub.2 SO.sub.4 and the solvent was removed under reduced pressure to given an orange **oil**. UV (CH.sub.3 OH) 214 nm, 358 nm. Anal. calc. for C.sub.20 H.sub.24 N.sub.2 O.sub.5 O: C, 64.52; H, 6.45; N,. . .

DETD . . . MgSO.sub.4. The ether layer was decanted from the drying agent and the solvent was removed under reduced pressure. To the **oil** residue, ether was added and then removed (10.times.5 ml) on a vacuum pump. A foam was formed, which returned to an **oil** upon exposure to the atmosphere. Structure was confirmed by NMR analysis.

DETD GABA (4 g, 38.8 mmol) was suspended in 50 ml (0.48 mol) of **benzyl alcohol**. The reaction mixture was stirred, with cooling on an ice bath, while 20 ml SOCl.sub.2 was added dropwise over a. . .

DETD . . . extracted into ethyl acetate and dried over Na.sub.2 SO.sub.4. Evaporation of solvent left the desired product as a sticky yellow **oil**. Identity of the product, which has the structural formula ##STR1569## was confirmed by NMR analysis.

DETD . . . to the reflux temperature. The mixture was refluxed for 3 hours, then stirred overnight. Evaporation of solvent left a yellow **oil** which crystallized and which was recrystallized from acetone/ethyl ether. The light yellow crystals thus obtained were collected by filtration and. . .

DETD . . . dihydro compound, was separated from the aqueous layer and dried over Na.sub.2 SO.sub.4. Evaporation of ethyl aetate left a yellow

oil which reduced methanolic silver nitrate immediately. UV and NMR analysis confirmed the identity of the product, which has the formula. . .

DETD . . . was allowed to gently reflux overnight. Filtration of a white precipitate and evaporation of the yellow filtrate produced a reddish **oil**, which was dissolved in acetone, filtered and evaporated to dryness. Anal. calc. for C.sub.22 H.sub.23 O.sub.3 N.sub.2 I: C, 47.26;. . .

DETD . . . the mixture was stirred under nitrogen for 30 minutes. The organic layer was extracted and dried to give an orange **oil** that reduced methanolic silver nitrate immediately. NMR analysis confirmed that the product has the structure: ##STR1571##

DETD . . . Using an ice-water cooled condenser, the mixture was brought to a gentle reflux and refluxing was continued overnight on an **oil** bath. Thin layer chromatography confirmed that the resulting dark orange solution was the desired product. Addition of CH.sub.3 CN and. . .

DETD . . . layers were separated and the yellow organic layer was dried over sodium sulfate and evaporated to dryness. The resulting yellow **oil** reduced methanolic silver nitrate immediately. The structure of the product was confirmed by NMR analysis to be: ##STR1573##

DETD . . . and the solution was stirred for 4 hours. The organic layer was dried and evaporated to dryness, leaving a yellow **oil** which reduced methanolic silver nitrate immediately. The product has the formula: ##STR1574##

DETD 5,5-Diphenyl-3-hydroxymethyl-2,4-imidazolidinedione (2 g, 0.0071 mol) was dissolved in bromoacetylchloride (15 g, 8 ml, 0.096 mol) by heating in an **oil** bath (70.degree.-80.degree. C. bath temperature) for about 15 minutes, until the formation of HCl ceased. The mixture was cooled and. . .

DETD . . . was dissolved in 2-bromopropionyl chloride (8.5 g, 5 ml, 0.05 mol) by heating for 30 minutes on a 100.degree.-110.degree. C. **oil** bath. The reaction mixture was cooled, 20 ml of ethyl ether were added, and the resultant solution was extracted with. . .

DETD . . . ml of nitromethane was mixed with nicotinamide (0.61 g, 0.005 mol). The solution was stirred on a 90.degree.-100.degree. c. temperature **oil** bath for 2 hours. The mixture was cooled to 60.degree.-70.degree. C. and the white crystals which had formed were removed. . .

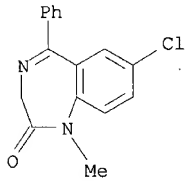
DETD . . . g, 0.4 ml, 0.006 mol) was added and the mixture was warmed for 2 hours at 70.degree. C. on an **oil** bath. Removal of solvent by vacuum distillation afforded a yelllow crystalline product melting at 110.degree.-115.degree. C. Yield 100% (0.54 g).. . .

DETD . . . a build-up of the concentration of the intermediate charged species (quarternary form) in the brain even after one single bolus **injection** of the starting **lipophilic** chemical delivery system (dihydro form). There is a first portion of the brain level versus time curve which shows a. . .

=>

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 439-14-5 REGISTRY
CN 2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-1-methyl-5-phenyl- (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-Methyl-5-phenyl-7-chloro-1,3-dihydro-1H-1,4-benzodiazepin-2-one
CN 1-Methyl-5-phenyl-7-chloro-1,3-dihydro-2H-1,4-benzodiazepin-2-one
CN 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one
CN 7-Chloro-1-methyl-2-oxo-5-phenyl-3H-1,4-benzodiazepine
CN 7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one
CN 7-Chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one
CN Alboral
CN Aliseum
CN Alupram
CN Amiprol
CN An-Ding
CN Anlin
CN Ansiolin
CN Ansiolisina
CN Antenex
CN Anxionil
CN Apaurin
CN Apo-diazepam
CN Apozepam
CN Armonil
CN Arzepam
CN Assival
CN Atensine
CN Atilen
CN Azedipamin
CN Baogin
CN Benzopin
CN Best
CN Betapam
CN Bialzepam
CN Britazepam
CN Calmocitene
CN Calmod
CN Calmpose
CN Caudel
CN Centrazepam
CN Cercine
CN Ceregulart
CN Chuansuan
CN D-Pam
CN Desconet
CN Desloneg
CN Diacepan
CN Diaceplex
CN Dialag
CN Dialar
CN Diapam
CN Diapax
CN Diapine
CN Diaquel
CN **Diazepam**
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
FS 3D CONCORD
DR 11100-37-1, 53320-84-6

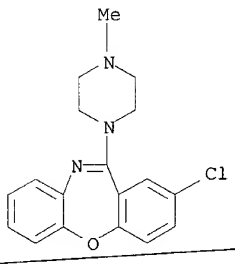
MF C16 H13 Cl N2 O
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGPAT, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11423 REFERENCES IN FILE CA (1962 TO DATE)
59 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
11431 REFERENCES IN FILE CAPLUS (1962 TO DATE)
55 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L5 ANSWER 134 OF 134 REGISTRY COPYRIGHT 2002 ACS
RN 1977-10-2 REGISTRY
CN **Dibenz[b,f][1,4]oxazepine, 2-chloro-11-(4-methyl-1-piperazinyl)-(7CI, 8CI, 9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine**
CN **2-Chloro-11-(4-methylpiperazino)dibenz[b,f][1,4]oxazepine**
CN CL 62362
CN **Cloxazepine**
CN HF 3170
CN Loxapin
CN Loxapine
CN LW 3170
CN Oxilapine
CN S 805
CN SUM 3170
FS 3D CONCORD
MF C18 H18 Cl N3 O
CI COM
LC STN Files: ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CHEMCATS, CHEMLIST, CIN, DDFU, DIOGENES, DRUGPAT, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PROMT, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

329 REFERENCES IN FILE CA (1962 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
329 REFERENCES IN FILE CAPLUS (1962 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>